From:	Marco Troiani
To:	cac@Cannabis
Cc:	Marc Whitlow; Debby Goldberry
Subject:	Public Comment for 9/19 CAC Meeting
Date:	Wednesday, September 18, 2024 7:40:38 AM
Attachments:	20240313_Cannabinoid_Inflation_Whitepaper.pdf The-federal-recreational-hemp-phenomenon.pdf 20240918_hemp_adulteration_proposal.pdf

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[EXTERNAL]: marco@digammaconsulting.com

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Hello CAC Team,

I am writing to submit our public comments on the issues relating to the cannabis industry, particularly the following:

1. Cannabis lab fraud and cannabis inflation.
Filename: **20240313_Cannabinoid_Inflation_Whitepaper.pdf**

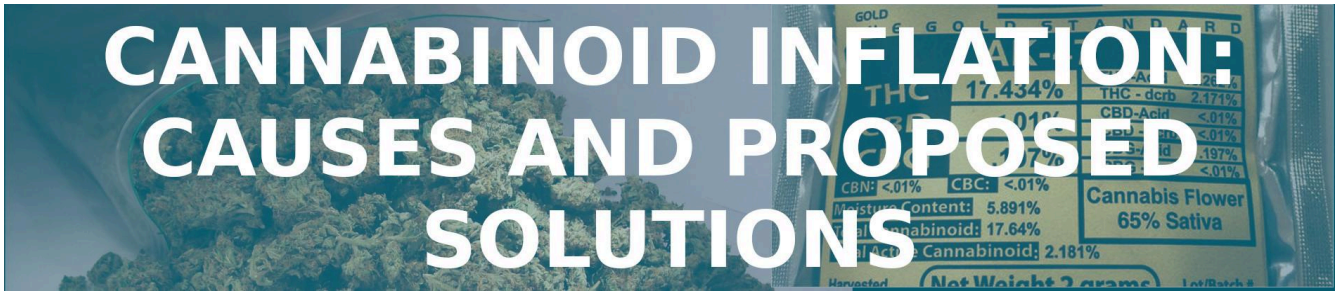
2. Federal Recreational Hemp phenomenon competing without taxes or safety testing.
Filename: **The-federal-recreational-hemp-phenomenon.pdf**

3. Synthetic d9-THC derived from hemp adulterating state-licensed cannabis products and testing to prevent this adulteration: Filename: **20240918_hemp_adulteration_proposal.pdf**

Please let us know if you need anything else from us or if there is anything we can help clarify.

Cheers,

Marco Troiani
CEO & Co-Founder
Digamma Consulting
marco@digammaconsulting.com



Abstract

The cannabis industry faces a pervasive challenge known as cannabinoid inflation, where testing laboratories provide inaccurately high cannabinoid concentrations to win business, threatening the existence of legitimate labs. Digamma Consulting, seasoned experts in cannabis chemistry, proposes practical, low-cost regulatory solutions to address this issue. Solutions include Suspect Product Checks, Chemical Analysis, Laboratory Audits, and Data Analysis Reports. These measures aim to ensure accurate testing standards, protect public safety, and enhance consumer confidence. This white paper outlines the urgency of resolving cannabinoid inflation for the development of a safe, fair, and thriving cannabis industry.

Introduction

The cannabis industry is at a pivotal juncture where manipulations of testing data threaten consumer safety, regulatory compliance, and market fairness. Amidst this landscape, Digamma Consulting, recognized as a seasoned and impartial expert in cannabis chemistry, endeavors to address a critical challenge plaguing the sector: cannabinoid inflation. This white paper serves as a comprehensive elucidation of the issue, coupled with solutions aimed at empowering government regulators to ensure transparency, impartiality, and legal defensibility in cannabis testing reporting and labeling.

Cannabinoid inflation, an unfortunately prevalent phenomenon, sees cannabis testing laboratories furnishing inaccurately high cannabinoid concentrations in a bid to secure business. This practice distorts market competition and poses a grave threat to legitimate testing facilities, which cannot compete with inflated results. As dispensaries gravitate

towards labs offering higher THC values, the industry witnesses a concerning trend of laboratory shopping, exacerbating the problem further.

For this white paper, Digamma Consulting draws from over twelve years of experience since establishing the nation's pioneer cannabis testing lab and through working with 48 labs in 16 states. Since 2011, Digamma has witnessed the escalation of the cannabinoid inflation issue across the United States. The repercussions extend beyond economic concerns, impinging upon public safety and consumer confidence. And the related issue of contamination deflation is equally concerning, as the same labs inflating cannabinoids may be under-reporting problems. Digamma advocates adherence to rigorous testing standards similar to those stipulated by the United States Environmental Protection Agency (USEPA), renowned for their stringency and legal defensibility, to counteract this alarming trend.

Cannabinoid inflation, left unchecked, not only jeopardizes the viability of conscientious labs but also poses a significant liability for medical patients reliant on accurate cannabinoid labeling for appropriate dosing. The imperative to address this challenge is underscored by its ramifications for developing a safe, fair, and thriving cannabis industry both domestically and internationally.

In response to this pressing issue, Digamma proffers three comprehensive solutions tailored for government regulators:

- **Solution A: Data Analysis Report:** Advocating for the adoption of data analysis reports, providing a firm basis for regulatory action.
- **Solution B: Suspect Product Checks (Secret Shopper):** Proposing a cost-effective mechanism for states to conduct sampling and testing of products at accredited reference laboratories to detect inflated cannabinoid values.
- **Solution C: Chemical Analysis Laboratory Audits:** Recommending audits by chemical analysis experts to regulate issues of cannabinoid inflation and ascertain the veracity of testing data.

Accompanying this white paper are appendices delving into the technical intricacies of cannabinoid inflation and Digamma's extensive experience in cannabis analysis. The ultimate goal of this endeavor is to bolster consumer safety and confidence, thereby fostering trust in cannabis and its regulatory framework. We invite further discussion and collaboration to address this critical issue and propel the cannabis industry toward a future characterized by integrity, transparency, and accountability.

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Solution A – Data Analysis Reports

Data analysis reports are a low-cost technique for state regulators to process existing data collected in their jurisdiction and to see patterns that indicate manipulation. The methodology is similar to what occurs on the final results reports for the Emerald PT Report, which shows the accuracy and precision of the participating labs for a given analysis.

Accuracy is typically shown against a known true value for a PT sample, but the same concept applies when Certified Reference Materials (CRM) are used for a round-robin style assessment of laboratory accuracy. It is generally shown as a percent recovery of the true value.

Precision is typically shown against the distribution of reported results for the same analyzed sample across participating labs. Through this method, the performance of laboratory precision is weighed relative to the group's performance as a whole and is typically represented as a Z-score value for each participant. Z-scores is the number of standard deviations a value is from the mean, indicating whether a laboratory is within the average or is an outlier.

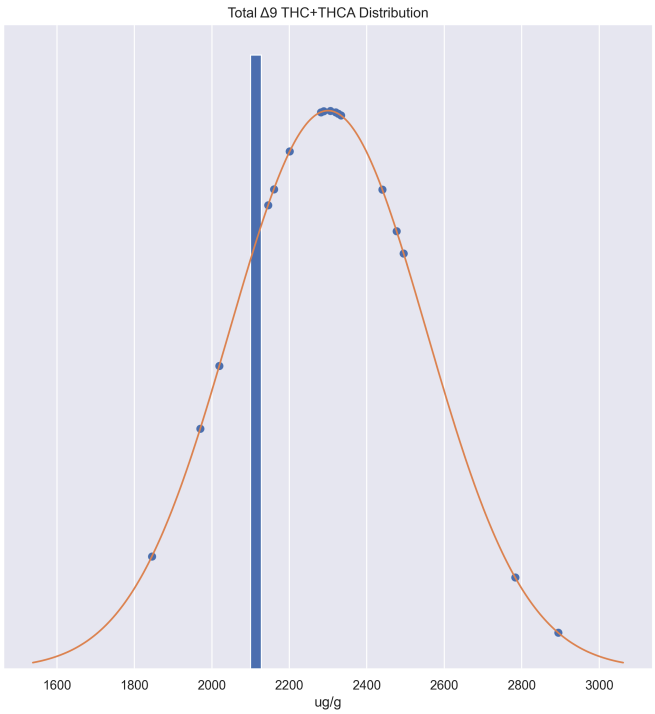

Chart 01 – This chart shows a sample of a normal distribution curve of total THC results for a PT round between cannabis testing labs. The blue line is the true value of the sample sent out for analysis, and the curve shows the distribution of reported results. It documents a median higher than the true value, which supports the hypothesis of cannabinoid inflation in reported results by testing labs. The chart is connected to Solution A.

When a combination of accuracy and precision is well illustrated for a large data set collected from a given jurisdiction, patterns such as cannabinoid inflation and contaminant suppression become visible on a larger scale. The push of THC numbers up above 20%, a significant selling point for cannabis products, becomes visible in the data distributions and can indicate an issue of laboratory data accuracy. This same trend is seen with contaminants, which show a high probability of data manipulation when reported values are just below an action level and are more common than the surrounding values.

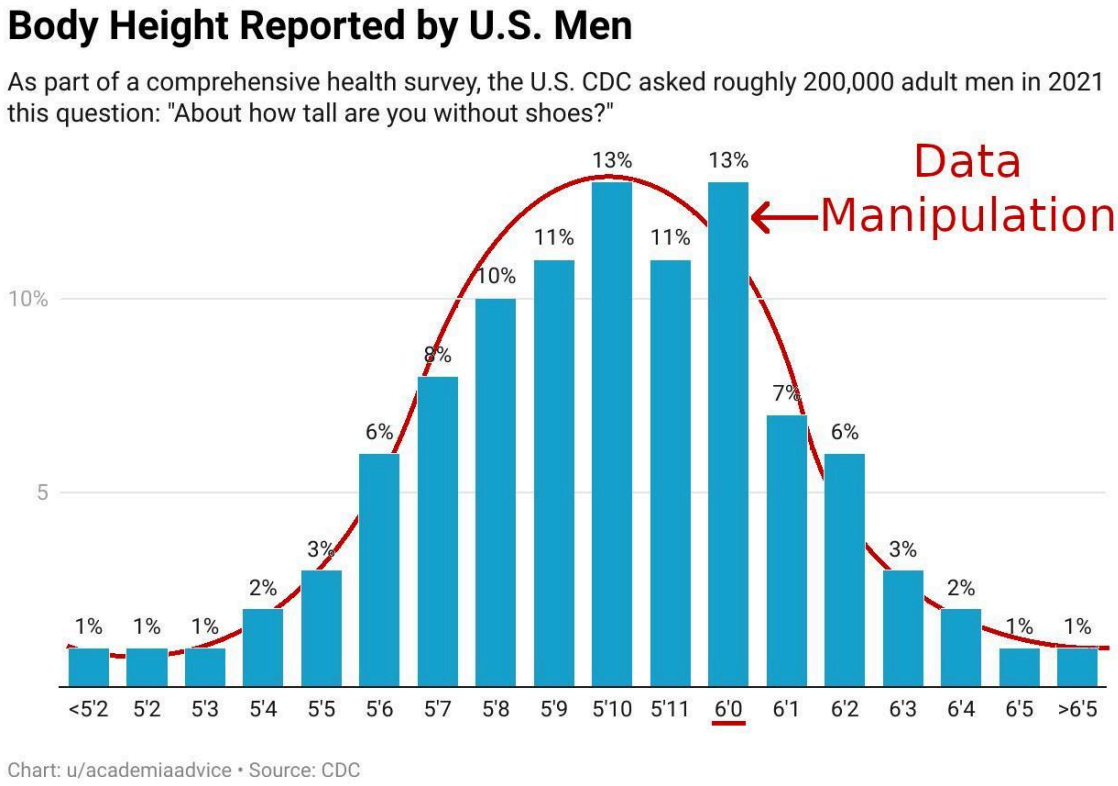

Chart 02 – This chart is a sample of a normal distribution curve of the total height of American men. This distribution shows the sampling bias that men who are 5’11 will often report that they are 6'0, creating a noticeable disruption from the normal distribution at 6 '0. This trend and its exceptions are outlined in red. This chart is connected with Solution A.

While Digamma believes this type of data analysis is the easiest, quickest, and lowest cost method to find data manipulation, it lacks some of the more systematic approaches outlined in Solutions 1 and 2 above. Some articles listed in Appendix 1 use this technique to help illustrate the problem of relying wholly on data analysis reports. This technique could be more effective in partnership with regulators with a larger data set size, giving state regulators valuable information as a basis for decisions and actions.

Solution B - Suspect Product Checks (Secret Shopper) Program

The essential element needed to prevent cannabinoid inflation is objective and reliable data that can be used to assess the claims of products on shelves in licensed dispensaries. With this data, the state regulators would have accurate and reliable information to use as a basis for enforcement actions.

The traditional method that many states have used to verify cannabis testing laboratory's competency has been ISO/IEC 17025:2017 accreditation. Although this accreditation is a strong indicator of competency of an analytical laboratory in many industries, ISO/IEC 17025:2017 does not prescribe measurement accuracy. This may be due to a lack of regulatory knowledge or the limited scope of ISO/IEC 17025:2017 assessments by accreditation bodies such as Perry Johnson Laboratory Association (PJLA), American Association for Laboratory Accreditation (A2LA), and ANSI National Accreditation Board (ANAB), three primary groups commonly used for cannabis laboratory accreditation. Regardless of the causes, the practical effect is that ISO/IEC 17025:2017 accreditation alone cannot verify laboratory accuracy in the cannabis industry.

Currently, the standard to determine competency for cannabis testing laboratories is ISO/IEC 17025:2017 accreditation. Although this accreditation is a strong indicator of reliable performance in many industries employing standardized methods, ISO/IEC 17025:2017 accreditation does not specify or prescribe precision for internally validated methods. Please reference ISO/IEC 17025:2017 Section 7.2 for validation requirements. Variability in results may be due to a lack of consensus methods for lot designation, sampling technique, subsampling and homogenization technique, test method specifications such as gravimetric vs volumetric dilutions. Furthermore, some states do not require that all methods/analytes/matrices are accredited. For example in New York the lab can be ISO/IEC 17025:2017 accredited for 'filth and foreign materials' and not even have cannabinoid quantification on the scope of their accreditation. Additionally a laboratory can list 'cannabis products' as the matrix which is

non-specific and creates gaps in the regulatory framework which can be used for data manipulation.

The next method to verify laboratory accuracy on cannabinoid results is proficiency testing (PT) programs. ISO 17025:2017 accreditation requires participation in a 3rd party PT program, in which a PT administrator sends a blind sample with a known concentration to all participating labs. In turn the labs test the sample and return their results to the administrator and are analyzed for accuracy. The results are compared to the known concentration and the labs are graded accordingly. The *Emerald PT Report* is one of the most extensive PT programs in the cannabis industry, which is a program that Emerald Scientific and Digamma operate in partnership.

PT program reports are ideal for catching inaccuracies in laboratory reporting that may not be intentional, such as inadequate contaminant testing (pesticides, metals, etc.). However, PT programs cannot demonstrate deliberate cannabinoid inflation because labs can provide the most accurate value when participating in a PT program and return to creating higher values when reporting client sample results. While the PT programs are ideal for demonstrating laboratory competence, they are poorly suited to catch intentional cannabinoid inflation.

Thus, a program is needed to collect data on cannabinoid inflation when performed intentionally. Digamma suggests a **Suspect Product Checks Program** where products on the shelves for consumer purchase are collected by secret shoppers and analyzed by a state reference lab. The reason a state reference lab is critical for the success of this program is because of the need for transparency and independence of the data being generated. Some states have attempted to use “Round Robin” style testing where they send a sample to many private laboratory licensees, and this practice is neither independent nor transparent and a poor basis for enforcement actions by regulators, as often a “Round Robin” style testing will show consistently inflated cannabinoid values across all participating laboratories. The values from this independent state analysis are compared with the label values, and this information is used to measure the amount of inflation. This procedure bypasses the issue in PT programs, where labs

intentionally inflating cannabinoid concentrations can evade detection. The program works because the comparison is done with samples of actual cannabis consumer goods and products without the lab's knowledge beforehand.

	Suspect Product Check (State Ref Lab)	**Laboratory Results** (Private Lab Licensee)	**Product Label** (Dispensary Off-The-Shelf)
Results	20 %Wt	30 %Wt	33 %Wt
Percent Recovery	100%	150%	165%

Chart 03 – This section describes how data will be collected from the producer and/or lab, and how it will be analyzed. The product's labeled value or the lab's test results are divided by Suspect Product Check results to create a percent recovery value. Findings of 100% represent an exact match with the Suspect Product Check value, and numbers over 100% show at least some degree of cannabinoid inflation.

MODEL SECRET SHOPPER PROGRAM: SAMPLE DATA (MASTER)

ID	Product		Producer			Laboratory			Dispensary		Cannabinoid Value %		
Item No.	Strain Name	Tracking	Licensee	Tracking	Harvest Date	Licensee	Tracking	Test Date	Licensee	Tracking	Label Claim	Ref Lab	Deviation
10000001	Girl Scout Cookies	9611823534	Cultivation A	6392722369	2023-10-19	Laboratory A	5782580048	2023-10-26	Dispensary A	9534612790	24.6	18.3	134.43%
10000002	Gorilla Glue#4	2902526966	Cultivation B	5173698149	2023-10-23	Laboratory B	8484312834	2023-10-30	Dispensary B	6132526878	30.9	23.8	129.83%
10000003	Kosher Kush	453878671	Cultivation C	869184210	2023-10-30	Laboratory C	1461999850	2023-11-06	Dispensary C	7465780042	22.6	21.0	107.62%
10000004	Pineapple Express	3569673124	Cultivation D	4018053641	2023-11-02	Laboratory A	9897256588	2023-11-09	Dispensary D	6287247087	25.6	18.9	135.45%
10000005	Bubba Kush	9194313205	Cultivation E	1267487049	2023-11-05	Laboratory C	8773395409	2023-11-12	Dispensary E	1533602850	17.1	17.2	99.42%
10000006	Strawberry Cough	8520341307	Cultivation F	948345584	2023-11-09	Laboratory A	2412781265	2023-11-16	Dispensary F	9057841562	23.1	17.3	133.53%
10000007	Super Lemon Haze	8979567936	Cultivation G	2580404151	2023-11-13	Laboratory B	2954793189	2023-11-20	Dispensary G	6928887923	21.6	19.2	112.50%
10000008	Vanilla Kush	7568298316	Cultivation H	2673905882	2023-11-17	Laboratory D	5747764217	2023-11-24	Dispensary H	8671825504	23.9	15.9	150.44%
10000009	Lemon Cookies	154715828	Cultivation A	2027593221	2023-11-22	Laboratory C	5263211502	2023-11-29	Dispensary A	705014519	22.1	20.9	105.74%
10000010	Sour Diesel	6727488980	Cultivation B	6124270972	2023-11-25	Laboratory D	6435701172	2023-12-02	Dispensary B	398207347	33.2	21.8	152.29%
10000011	Acapulco Gold	7851915805	Cultivation C	2435083626	2023-11-27	Laboratory B	4242183304	2023-12-04	Dispensary C	8493243699	25.0	20.9	119.62%
10000012	Pineapple Love Bomb	2172175085	Cultivation D	5361844329	2023-11-30	Laboratory C	8007588246	2023-12-07	Dispensary D	5024359848	25.0	22.9	109.17%
10000013	Jack Herrer	6302236166	Cultivation E	7407316304	2023-12-02	Laboratory D	7933222106	2023-12-09	Dispensary E	7440888906	32.0	20.2	158.42%
10000014	Cookie Monster	8831333112	Cultivation F	6609285559	2023-12-05	Laboratory A	1951891606	2023-12-12	Dispensary F	4506279111	28.2	20.9	134.93%
10000015	OG Kush	3032392685	Cultivation G	1774025462	2023-12-09	Laboratory B	7143040573	2023-12-16	Dispensary G	1688426893	25.0	19.9	125.63%

Legend	<+10%	<+20%	<+30%	>+30%

Chart 04 – This chart represents a sample data set showing the concepts outlined for Solution B – Suspect Product Check (Secret Shopper) Program. Data is shown as a master data list collected across the jurisdiction.

MODEL SECRET SHOPPER PROGRAM: SAMPLE DATA (BY LABORATORY)

Laboratory A

ID	Product		Producer			Laboratory			Dispensary		Cannabinoid Value %		
Item No.	Strain Name	Tracking	Licensee	Tracking	Harvest Date	Licensee	Tracking	Test Date	Licensee	Tracking	Label Claim	Ref Lab	Deviation
10000001	Girl Scout Cookies	9611823534	Cultivation A	6392722369	2023-10-19	Laboratory A	5782580048	2023-10-26	Dispensary A	9534612790	24.6	18.3	134.43%
10000004	Pineapple Express	3569673124	Cultivation D	4018053641	2023-11-02	Laboratory A	9897256588	2023-11-09	Dispensary D	6287247087	25.6	18.9	135.45%
10000006	Strawberry Cough	8520341307	Cultivation F	948345584.4	2023-11-09	Laboratory A	2412781265	2023-11-16	Dispensary F	9057841562	23.1	17.3	133.53%
10000014	Cookie Monster	8831333112	Cultivation F	6609285559	2023-12-05	Laboratory A	1951891606	2023-12-12	Dispensary F	4506279111	28.2	20.9	134.93%
												Laboratory A Average	134.58%

Laboratory B

ID	Product		Producer			Laboratory			Dispensary		Cannabinoid Value %		
10000002	Gorilla Glue#4	2902526966	Cultivation B	5173698149	2023-10-23	Laboratory B	8484312834	2023-10-30	Dispensary B	6132526878	30.9	23.8	129.83%
10000007	Super Lemon Haze	8979567936	Cultivation G	2580404151	2023-11-13	Laboratory B	2954793189	2023-11-20	Dispensary G	6928887923	21.6	19.2	112.50%
10000011	Acapulco Gold	7851915805	Cultivation C	2435083626	2023-11-27	Laboratory B	4242183304	2023-12-04	Dispensary C	8493243699	25.0	20.9	119.62%
10000015	OG Kush	3032392685	Cultivation G	1774025462	2023-12-09	Laboratory B	7143040573	2023-12-16	Dispensary G	1688426893	25.0	19.9	125.63%
												Laboratory B Average	121.89%

Laboratory C

ID	Product		Producer			Laboratory			Dispensary		Cannabinoid Value %		
10000003	Kosher Kush	453878670.7	Cultivation C	869184209.8	2023-10-30	Laboratory C	1461999850	2023-11-06	Dispensary C	7465780042	22.6	21.0	107.62%
10000005	Bubba Kush	9194313205	Cultivation E	1267487049	2023-11-05	Laboratory C	8773395409	2023-11-12	Dispensary E	1533602850	17.1	17.2	99.42%
10000009	Lemon Cookies	154715828.3	Cultivation A	2027593221	2023-11-22	Laboratory C	5263211502	2023-11-29	Dispensary A	705014518.7	22.1	20.9	105.74%
10000012	Pineapple Love Bomb	2172175085	Cultivation D	5361844329	2023-11-30	Laboratory C	8007588246	2023-12-07	Dispensary D	5024359848	25.0	22.9	109.17%
												Laboratory C Average	105.49%

Laboratory D

ID	Product		Producer			Laboratory			Dispensary		Cannabinoid Value %		
10000008	Vanilla Kush	7568298316	Cultivation H	2673905882	2023-11-17	Laboratory D	5747764217	2023-11-24	Dispensary H	8671825504	23.9	15.9	150.44%
10000010	Sour Diesel	6727488980	Cultivation B	6124270972	2023-11-25	Laboratory D	6435701172	2023-12-02	Dispensary B	398207346.5	33.2	21.8	152.29%
10000013	Jack Herrer	6302236166	Cultivation E	7407316304	2023-12-02	Laboratory D	7933222106	2023-12-09	Dispensary E	7440888906	32.0	20.2	158.42%
												Laboratory D Average	153.72%

Legend	<+10%	<+20%	<+30%	>+30%

Chart 05 – The chart represents a sample data set showing the concepts outlined for Solution B – Suspect Product Check (Secret Shopper) Program. It has been reformatted to show individual laboratory trends in deviation value for cannabinoid inflation.

See above for an example generated with model data for a hypothetical Suspect Product Checks Program. It models how the data would be collected and tracked to the cultivator, manufacturer or distributor, lab, and dispensary and compared to the reference laboratory concentrations on the product label. The report generates an accuracy percentage showing the inflation of THC or other cannabinoids in the examined samples. It can easily be organized by laboratories or any other party to see trends in inflation averages within this subset.

For a Suspect Product Check Program to have an objective value for comparison to label claims, an independent laboratory must perform the cannabinoid analysis for the state regulators. For the laboratory to be accurate enough for use by regulators, it must be validated not only to levels of the ISO 17025:2017 program but also to standards used in EPA and FDA analysis laboratories. This level of validation provides the legal defensibility of analytical data necessary for

use in state regulations and legal proceedings. This methodology can be accomplished with a validation of the analytical method that complies with standards outlined by federal regulatory agencies.

Additionally, the state's cost of such an analysis is relatively low. While many licensed cannabis testing labs spend about $2 million on their analytical equipment for a complete set of seven instruments, a state-associated cannabinoid analysis laboratory would only need one instrument to set the whole laboratory up for a much lower cost. Establishing a Suspect Product Check Program is a critical and necessary tool for state regulators to collect data at an affordable rate, especially when other costs, such as laboratory space and staff, can be merged with existing state laboratory resources.

Upon request, Digamma can outline cannabinoid testing equipment costs and the total costs of working together to establish and validate a functioning cannabinoid analysis lab.

Solution B2 – Legal Defensible Data For State Reference Lab

The critical variable in any regulatory or legal challenge is creating and maintaining defensible chemical analysis data to use as a basis for enforcement and to defend against outside parties. Diagrams outline Digamma’s validation style and its roots in EPA compliance for serious contaminants hazardous to public health in Solution C. It is worth noting that data from the accredited reference laboratory used by the state for Solution B, outlined below, is critical and necessary for any laboratory compliance program's success.

Expanded uncertainty is the critical variable that any laboratory needs for defensibility in the broadest sense. Expanded uncertainty is a value calculated using the variations of each measurement in a process, which gives a range of variation for the final reported results. Expanded uncertainty calculations must be pegged to traceability to the International System of Units for legal defensibility.

Other variables include scale calibration, scale verification, pipette calibration, pipette

verification, and quality logs relating to uncertainty measurements, including temperature, frequency, centrifugal force, and solvent/reagent purity verification. These variables must comply with the relevant chemical analysis standards. Thus, the essential elements of tracking expanded uncertainty have a downstream influence on direct calibration metrics, such as instrument calibration curves, linear dynamic ranges, extraction efficiency, and matrix interference, including ion suppression and amplification phenomena that may affect the accuracy of the final reported results. More information on Digamma's thoughts on legal defensibility and the general accuracy of cannabis analysis labs is in Appendix 3. This can help generate the most defensible data for the state.

Because the elements addressed here are technical, Digamma feels that sharing our complete validation reports with technical parties within your department may be the best way to communicate the methodologies we have adapted from the EPA for quality control and legal defensibility in cannabis testing laboratories. These documents include validations of every analytical method operated by a cannabis analysis laboratory in 16 U.S. states on every major instrument manufacturer (PerkinElmer, Agilent, Waters, Thermo, Shimadzu) since 2011.

Digamma would happily share this information with any Government regulator after signing a non-disclosure agreement (NDA). We ask that these documents not be published because they represent over a decade of scientific and regulatory development work, and their public release would be detrimental to our organization. Please let us know if your institution is interested in reviewing this information.

Solution C – laboratoryAudits

laboratory audits are essential to address the cannabinoid inflation enforcement problem. Even when a standardized method is enforced uniformly, such as those California's DCC required in 2023, the labs can still manipulate data to produce inflated results for their clients in ways that can only be detected by a direct audit.

In this environment, as in the environment-related industry, auditing laboratories are needed to ensure that regulated laboratories are not committing fraud. Even when the data packets shared with the state show all of the calculations, calibrations, and quality control samples (standard in most states for cannabis testing and mandatory for all EPA and FDA-licensed labs), other elements can be used to manipulate the results. Some of these are covered in the 2016 ACS article on cannabinoid inflation and its technical basis, found in Appendix 1. A thorough audit by experienced laboratory chemists, who are familiar with such manipulations, would be considerably deeper in scope, which Digamma has outlined in Appendix 2. Manipulations range from changes to calibration standards to modifications of data analysis and would not be evident from the data packets submitted to the state.

A thorough audit would ensure that all quality control data from the data packet is available, can be traced to the data source, and includes all components that may be used to alter the final reported data. These components include but are not limited to scale calibration, standard calibration procedure and frequency, instrument maintenance and frequency, sample prep extraction, data analysis, and final results reported calculations.

Digamma can develop a thorough quality management systems (QMS) auditing program to exclude the possibility of compliant testing labs performing these manipulations. This process allows enforcement to be applied equally throughout a given jurisdiction, with qualified audit staff to perform laboratory audits as needed. It can be organized with regulatory oversight in diverse formats, ranging from supporting the establishment and training of the current state personnel for conducting these audits to outsourcing the task to a proficient private firm capable of executing them. In Appendix 2, Digamma outlines the most critical variables affecting cannabinoid inflation audits. For more general details about the QMS program, see Appendix 3.

Charts 6 and 7 below contain a sample of the validation protocols based on EPA standards that Digamma has been using to help labs get licensed through proper method validation. It includes validation of accuracy, precision, detection limits, matrix extraction efficiency, known interferences, and independent reproducibility and robustness.

[redacted]

Validation of Cannabinoid Analysis by HPLC-UV in Cannabis species plants and their derivative products

Lab Director: [redacted]
Lab Technician:

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Reviewed and Approved:

_____ _____
[redacted] Date
Lab Director Signed

Chart 06 – This chart is an outline of sample validations of 14 cannabinoids in the state of Missouri in late 2022, with sections and chapters of the validation report indicated to show its breadth. It is connected to Solutions 1B and 2.

SUMMARY

1. SCOPE

A validation study was performed for the analysis of cannabinoids by High Performance Liquid Chromatography with UV detection (**HPLC-UV**). The analytical method was validated in three phases. In the first phase, **linearity and range**, method calibration R^2, LOD, and LOQ values were derived and compared with regulatory requirements. In the second phase, **matrix spike replicates** were performed for each class of matrix analyzed by the method and data was compared to regulatory requirements. In the third phase, **robustness**, an "unknown" sample was analyzed by different laboratory employees under varying external conditions and LQC results were compared with regulatory requirements. More details for each phase of the validation is demonstrated below.

This validation was performed with acceptance criteria based on the governing jurisdiction for analytical services, in this case the State of Missouri Department of Health and Senior Serives (19 CSR 30-95). The requirements are outlined in CSR laws and statutes, and have been summarized below:

- No less than 5 calibration points for generating calibration curves
- No less than 0.990 correlation coefficient (R^2) for each calibration curve
- Limits of Detection (LOD) and Limits of Quantification (LOQ) for each analyte must be experimentally derived with no less than 7 replicates
- Derived LOD and LOQ values must comply with CSR action levels for each analyte (1mg/g in sample)
- All Quality Control (QC) samples must comply with CSR specifications
  - $\pm$ 30% recovery on all matrix spike recovery QC samples
  - $\pm$ 30% on all continuing calibration verification (CCV) QC samples
  - $\leq$ 30% relative percent difference (RPD) on replicate QC samples
  - $\leq$ LOQ for all blank QC samples, including preparation blanks (PB) and calibration blanks (CB)

The most current version of this information can be found on the CSR website at:
https://health.mo.gov/safety/cannabis/

		CBDV	CBDA	CBGA	CBG	CBD	THCV	CBN	d9-THC	d8-THC	CBC	THCA
Calibration	More than 5 Calibration Points	TRUE	TRUE	TRUE	TRUE	TRUE	TRUE	TRUE	TRUE	TRUE	TRUE	TRUE
	Greater than 0.990 R2 value	TRUE	TRUE	TRUE	TRUE	TRUE	TRUE	TRUE	TRUE	TRUE	TRUE	TRUE
Replicates	7 or greater replicates	TRUE	TRUE	TRUE	TRUE	TRUE	TRUE	TRUE	TRUE	TRUE	TRUE	TRUE
	LOD and LOQ comply with regulations	TRUE	TRUE	TRUE	TRUE	TRUE	TRUE	TRUE	TRUE	TRUE	TRUE	TRUE
	Accuracy as measured by %recovery <30%	TRUE	TRUE	TRUE	TRUE	TRUE	TRUE	TRUE	TRUE	TRUE	TRUE	TRUE
	Precision as measured by %RPD <30%	TRUE	TRUE	TRUE	TRUE	TRUE	TRUE	TRUE	TRUE	TRUE	TRUE	TRUE
Matrix	Accuracy as measured by %recovery <30%	TRUE	TRUE	TRUE	TRUE	TRUE	TRUE	TRUE	TRUE	TRUE	TRUE	TRUE
	Precision as measured by %RPD <30%	TRUE	TRUE	TRUE	TRUE	TRUE	TRUE	TRUE	TRUE	TRUE	TRUE	TRUE
Robustness	LQC Passes Compliance Criteria for two or more laboratory staff	TRUE	TRUE	TRUE	TRUE	TRUE	TRUE	TRUE	TRUE	TRUE	TRUE	TRUE

Chart 07 - This is a report summary and outline of this sample validation of 14 cannabinoids in Missouri in late 2022, with sections and chapters of the validation report indicated to show the depth of focus for each validation component. It is critical to communicate the legal defensibility of the methodology, precisely as is used in

federally regulated testing, such as EPA and FDA. These ideas are connected to Solutions 1B and 2.

Digamma would happily share a copy of the entire validation document with a regulator or elected official upon request. The images in this section simply illustrate the data overview to show the validation's scope.

Additionally, Digamma would be happy to share documents on auditing cannabis analysis labs for more general audits with a broader scope. These may include concerns with **false negatives of severe contaminants** such as microbiology or pesticide analysis, whether due to error or manipulation. We believe that there is widespread under-reporting of contaminants in the cannabis supply chain at this time, based on our experience in the methodologies and practices of our extensive client list of laboratories analyzing cannabis. Although we believe the cannabinoid inflation issue is more pressing, due to its highly public nature and the effect it is having on consumer confidence in both the industry, supply chain safety, and regulatory framework, we believe the struggle to audit laboratories for proper reporting on contaminants to be a more important issue to pursue in the long run due to the serious health and safety implications it carries. Regardless of the deficiencies that currently exist in cannabis analysis laboratories, with proper education, monitoring, and enforcement **these problems can be easily solved**, to the benefit of the whole industry, with many of the solutions we are outlining. The more comprehensive audits may also include the scope of general laboratory accuracy and accountability with comparable standards in parallel analytical chemistry sectors and provide the state with more information on laboratory diligence and accuracy in reporting. This information can be found in Appendix 3.

Appendix 1: Media Articles Outlining Cannabinoid Inflation Issues

August 2016 - Variations in THC Reporting (From American Chemical Society 2016 Presentation by Digamma)
Part1 - http://growersnetwork.org/laboratories/variations-cannabinoid-reporting-part-one/

Part2 - http://growersnetwork.org/laboratories/variations-in-cannabinoid-reporting-part-two/

Part3 - http://growersnetwork.org/laboratories/variations-cannabinoid-reporting-part-three/

Part4 - http://growersnetwork.org/laboratories/variations-in-cannabinoid-reporting-part-four/

Part5 - http://growersnetwork.org/laboratories/variations-cannabinoid-reporting-part-five/

Part6 – http://growersnetwork.org/laboratories/variations-cannabinoid-reporting-part-six/

April 28th, 2017 - Leafly Investigation: Is Washington's Top Cannabis laboratory Inflating THC Numbers?
https://www.leafly.com/news/industry/leafly-investigation-washingtons-top-cannabis-lab-inflating-thc-numbers

February 1st, 2019 - Oregon marijuana regulators fail to meet even basic standards, state audit finds
https://www.oregonlive.com/news/2019/01/oregon-marijuana-regulators-fail-to-meet-even-basic-standards-state-audit-finds.html

January 27th, 2021 - Nevada cannabis testing lab targeted for passing tainted samples
https://mjbizdaily.com/nevada-cannabis-testing-lab-targeted-for-passing-tainted-samples/

June 29th, 2021 - America's Pot Labs Have A THC Problem
https://fivethirtyeight.com/features/americas-pot-labs-have-a-thc-problem/

September 15th, 2021 - HNHPC, INC. vs. THE DEPARTMENT OF CANNABIS CONTROL
https://mjbizdaily.com/wp-content/uploads/2021/09/Burner-distro-lawsuit.pdf

October 20th, 2021 - Study: Most Delta-8 THC Products Are Mislabeled—And Some Companies Are Faking Lab Results
https://www.forbes.com/sites/chrisroberts/2021/10/30/study-most-delta-8-thc-products-are-mislabeled-and-some-companies-are-faking-lab-results/?sh=4bd336dd7ec1

November 29th, 2021 - California rolls out plans to standardize cannabis testing statewide
https://mjbizdaily.com/california-rolls-out-plans-to-standardize-cannabis-testing-statewide/

June 16th, 2022 - Inaccurate strain names, poor labeling hinder marijuana industry, study shows
https://mjbizdaily.com/inaccurate-strain-names-poor-labeling-hinder-marijuana-industry/

July 1st, 2022 - DON PLUMLEE et al. v. STEEP HILL INC
https://mjbizdaily.com/wp-content/uploads/2022/07/Plumlee-v-Steep-Hill-Arkansas.pdf

July 25th, 2022 - 4 Arkansas marijuana companies hit with RICO suit over alleged THC inflation
https://mjbizdaily.com/4-arkansas-marijuana-companies-hit-with-rico-suit-over-alleged-thc-inflation/

July 28th, 2022 - The Inflated THC Crisis Plaguing California Cannabis
https://cannabisindustryjournal.com/feature_article/the-inflated-thc-crisis-plaguing-california-cannabis/

August 11th, 2022 - How cannabis testing labs help put undue focus on THC potency
https://mjbizdaily.com/how-cannabis-testing-labs-help-put-undue-focus-on-thc-potency/

August 17th, 2022 - Weed buyer beware: THC inflation is getting out of hand
https://www.leafly.com/news/science-tech/marijuana-thc-inflation-is-getting-out-of-hand

September 8th, 2022 - EXCLUSIVE: We tested top Calif. prerolls for potency inflation
https://www.weedweek.com/stories/exclusive-we-tested-top-calif-prerolls-for-potency-inflation/

October 17th, 2022 - Nevada marijuana lab disciplinary hearing further highlights industry's testing woes
https://mjbizdaily.com/nevada-marijuana-lab-disciplinary-hearing-further-highlights-industrys-testing-woes/

October 10th, 2022 - JASPER CENENO et al vs. DREAMFIELDS BRANDS INC. et al
https://www.dovel.com/wp-content/uploads/2022/10/Jeeter-complaint-FINAL.pdf

October 25th, 2022 - Marijuana company sued for not making customers high enough
https://www.cbsnews.com/news/cannabis-marijuana-dreamfields-jeeter-lawsuit-california-thc-high/

October 26th, 2022 - A California marijuana company is being sued over the potency of its joints
https://www.cnn.com/2022/10/26/business/california-marijuana-lawsuit-thc-trnd/index.html

October 31st, 2022 - Customers Sue California Marijuana Company For Overstating THC Potency In Its Joints
https://www.forbes.com/sites/dariosabaghi/2022/10/31/customers-sue-california-marijuana-company-for-overstating-thc-potency-in-its-joints/?sh=152309a93030

December 1st, 2022 - Dovel & Luner Sues V O Leasing Corp for Mislabeled THC Content
https://www.dovel.com/news/dovel-luner-sues-v-o-leasing-corp-for-mislabeled-thc-conent/

December 12th, 2022 - Valley Greens Retail Outlet, Inc et al. v. Savage Enterprises, et al.
https://www.insurancejournal.com/news/west/2022/12/08/698377.htm

January 13th, 2023 - More changes needed to address inflated THC levels

https://stratcann.com/insight/more-changes-needed-to-address-inflated-thc-levels/

March 21st, 2023 - Canadian cannabis industry reckons with inflated THC label claims
https://mjbizdaily.com/canadian-cannabis-industry-reckons-with-inflated-thc-label-claims/

April 12th, 2023 - Uncomfortably high: Testing reveals inflated THC potency on retail Cannabis labels
https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0282396

July 14th, 2023 - Organigram blames lower sales on THC inflation and no longer being able to sell “ingestible extracts”
https://stratcann.com/news/organigram-blames-lower-sales-on-thc-inflation-and-no-longer-being-able-to-sell-ingestible-extracts/

July 18th, 2023 - Organigram Blames ‘THC Inflation’ For Growing Losses and Falling Revenues in Q3
https://businessofcannabis.com/organigram-blames-thc-inflation-for-growing-losses-and-falling-revenues-in-q3/

August 2nd, 2023 - California Falls Short on Tracking Illegal Cannabis, Appellate Court Says
https://www.law.com/therecorder/2023/08/02/california-falls-short-on-tracking-illegal-cannabis-appellate-court-says/?slreturn=20231107172558

September 14th, 2023 - Valley Greens Retail Outlet, Inc et al v. Savage Enterprises, et al
https://www.scribd.com/document/678516992/37-2023-00041548-CU-BT-CTL-ROA-1-09-14-23-Complaint-1697654340880

September 20th, 2023 - NEW CALIFORNIA LAW AUTHORIZES LAWSUITS BY LICENSED CANNABIS BUSINESSES AGAINST UNLICENSED CANNABIS OPERATORS
https://www.omarfigueroa.com/new-california-law-authorizes-lawsuits-by-licensed-cannabis-businesses-against-unlicensed-cannabis-operators/

September 25th, 2023 - Legal cannabis labels inflate THC potency contained in products, executives say
https://www.theglobeandmail.com/business/article-dried-cannabis-labels-thc-content/

September 28th, 2023 - Accusations of Inflated THC Potency Surface in Canada
https://cannatechtoday.com/accusations-of-inflated-thc-potency-surface-in-canada/

October 26th, 2023 - Washington state suspends marijuana testing laboratory’s certification
https://mjbizdaily.com/washington-state-suspends-marijuana-testing-laboratorys-certification/

November 30th, 2023 - Marijuana lab-testing analysis finds routine THC inflation, data manipulation
https://mjbizdaily.com/marijuana-lab-testing-analysis-finds-routine-thc-inflation-data-manipulation/

December 1st, 2023 - Challenges and Considerations in OCS Addressing THC Inflation
https://www.linkedin.com/pulse/challenges-considerations-ocs-addressing-thc-inflation-jazz-samra-zmirc/?trk=public_post

December 5th, 2023 (date of access) - OrganiGram
https://inflated-thc.com/

December 20th, 2023 State cannabis regulators still one step behind questionable THC lab data
https://mjbizdaily.com/state-cannabis-regulators-still-one-step-behind-questionable-thc-lab-data/

Appendix 2: Outline of Cannabinoid Analysis laboratory Audit

A comprehensive laboratory audit protocol must be developed to establish uniform auditing standards across laboratories. This protocol is essential to guarantee the entire spectrum of cannabinoid analysis practices is addressed before conducting an audit of a licensed laboratory. Laboratory audits can exist on co-existing and overlapping levels, such as the prescriptive AOAC assessment which is overlapping with the ISO 17025:2017 assessment, as well as audits by local and state regulatory authorities that are typical for cannabis labs at this time.

Digamma has provided insights into key components utilized in the cannabinoid inflation industry. These crucial elements should be incorporated into any audit protocol designed to investigate this phenomenon in suspected laboratories. These components have been organized into specific topics, and Digamma has concisely described the practices to be scrutinized during an audit. The resulting information will contribute to an audit report delivered to the state, presenting comprehensive findings on the observed practices. Many states currently require provision of the ISO/IEC 17025:2017 assessment report by the laboratory to the regulator which may provide valuable insight.

Calibration / Reference Standard Manipulation

Audit Deliverable Purpose: To investigate the manipulation of calibration standards through degradation, improper dilution, and sourcing of less-than-reputable concentration standards.

Recommended Audit Actions: Audit calibration standard storage and handling procedure to ensure a lack of degradation. An audit of calibration curve standard preparation from the stock material purchased by the lab. A review of sources of calibration standards and their reliability for use as reference standards. Analysis of unopened, stored, and diluted calibration standards for quantitative comparison of concentrations used by the laboratory (can be done by the lab's equipment, by the state reference lab, or by portable devices brought on-site by auditors, e.g. spectrophotometer, IMS)

Note: ISO/IEC 17025:2017 already requires the use of accredited CRM when possible and requires verifications. However the acceptance criteria (related to continued use after opening or expiry) is determined by the laboratory's internally developed method and could be prescribed by a regulator.

Calibration Curve Manipulation

Audit Deliverable Purpose: To investigate manipulations of calibration curves, through extrapolated calibration curves, improper dilution steps in sample prep, and manipulations of the calibration curve.

Recommended Audit Actions: Audit of procedure for quantifying unknown samples using the validated method is declared Linear Dynamic Range (LDR). Derivation of LDR, calibration curve standard concentrations, LOQ and LOD values, and matrix recovery values will be reviewed and assessed for compliance and accuracy. Audit of sample prep process to evaluate for extraction efficiency, dilution procedure, and compliance with the method's declared LDR.

Sampling

Audit Deliverable Purpose: To investigate sampling procedure, including biased sampling of the batch or the laboratory representative sample, mis-weighing or mis-voluming in sample prep steps, or contamination of samples during prep.

Recommended Audit Actions: Audit of procedure outlining the sampling of batches, storing and transporting samples, sub-sampling batch samples in the laboratory, sample weighing and calibration, pipette use and calibration, inventory record keeping, and cross-contamination and adulteration prevention policies and practices. Inventory record keeping would demonstrate that labs may be prepping their samples with more than the mass listed in their calculations, giving higher values without further manipulating the data. Conducting an audit of product inventory tracking is essential to gather evidence of this practice. The only documented proof of this manipulation is consistently reflected in lower-than-listed inventory values, primarily observed in

the case of cannabis flower during testing.

Note: Sampling varies a lot between laboratories and even states. True random sampling of homogenous lots would be the 'most representative". Implementation consistently may pose an issue for established client-laboratory relationships which would have to be monitored by state regulators and this would be very hard to distinguish *during* any audit/assessment/direct observation, unless the regulator has & watches 'routine' surveillance.

Note: Calibration under ISO 17025:2017 for pipette balance 'inventory' is required. However, acceptance criteria for ongoing use & calibration schedule determine by laboratory is not under the 'ISO/IEC 17025:2017 clause' which would address an audit of product inventory. It is possible that balance or pipette has loose acceptance critera, which would have a destabilizing effect on the final uncertainty of the reported value. It is also possible that gravimetric versus volumetric dilutions may also trigger similar issues with data accuracy and provide opportunities for data manipulation.

Sampling Size, Homogenization, and Replication

Audit Deliverable Purpose: To investigate biased sub-sampling sizes, the use of replicates in a method that allows for reporting of the highest observed value, and any homogenization practice that would manipulate the final reported result, including contamination with target compounds.

Recommended Audit Actions: Audit of procedures outlining homogenization and sub-sampling of representative samples of the production batch performed in the analytical laboratory. The process includes examining the sub-sampling mass size, the policy and practice surrounding replicate analysis and its effect on reporting, and the homogenization procedure used in the laboratory. An audit of sampling size and its impact on replicate testing of the same batch of material would be used to indicate precision and repeatability. A significant variance combined with a policy of replicate testing by selecting a single or sub-section of results can easily give a higher-than-average reported value.

Note: Moisture is also largely an internally developed/validated which can have any MU - different laboratories employ different moisture technique/instrument with varying considerations for contributions to uncertainty leading to some labs using different temperatures. Many laboratories do not consider loss on volatiles such as terpenes which will have a negative effect on reported data accuracy.

Correction Factors - Mass

Audit Deliverable Purpose: To investigate the manipulation of mass-based correction factors, such as stem removal and moisture, and ensure that all correction factors are used accurately and uniformly and are not a source of errors or manipulation of reported results.

Recommended Audit Actions: Conduct an audit of procedures for sample preparation and reporting, emphasizing the selective removal of plant tissue, such as stems, and examining the correction factors employed by mass for moisture content. If a moisture content correction is performed in the method's reporting procedure, the moisture value can be a source of manipulation of cannabinoid results if it is not accurately derived. Excessive heating of samples for moisture content poses a risk of oxidation or carbonization, leading to inaccurately high moisture content values. Consequently, this can result in inflated cannabinoid content values after dry-weight correction. A thorough investigation of the moisture content derivation procedure is essential to address this issue. It entails auditing the process and scrutinizing all quality and validation data associated with deriving and reporting this value.

Correction Factors - Decarboxylation

Audit Deliverable Purpose: To investigate improper use of molecular mass conversions, such as those between THCA and THC and other cannabinoids and their corresponding acid forms. It would also review the manipulation of reported results by improper summation of values such as unrelated or antagonistic cannabinoids such as THC and CBD.

Recommended Audit Actions: An audit involves scrutinizing procedures for reporting final results,

focusing on calculated correction factors like cannabinoid acid decarboxylation and equivalent concentrations post-conversion.

Derivation of exact mass conversion factors used, either from regulations or scientific literature, and review of the policy of reporting combined, total, or potential cannabinoid concentrations are necessary to assess these conversion factors thoroughly.

Chromatographic Co-Elution

Audit Deliverable Purpose: To investigate the mis-integration of non-target compounds by the analytical method, including other cannabinoids and UV active compounds such as waxes that are common in the cannabis plant. It includes intentional allowance of target compound carry-over from one sample analysis to the next in the same instrument, inflated the final reported value relative to the amount present in the sample.

Recommended Audit Actions: Conduct an audit of chromatograms for target compounds to assess potential co-elution of other targets or matrix interferences that may affect the measured quantity of the target compound. It involves reviewing chromatograms, assessing column length and maximum resolution, evaluating instrument flush time and addressing carry-over contamination, and conducting a comprehensive matrix interference assessment.

Much of the audited procedures will be reviewed and compared to the declared values and procedures outlined in the method's validation report. Digamma has noted laboratories employing very short columns, approximately 50mm long, enabling co-eluting compounds to increase their reported values in matrix samples artificially. Strikingly, this manipulation does not impact solvent standard calibrations, often yielding compliant quality control sample data and proficient proficiency testing (PT) results for the lab. However, it results in consistently higher reported values for matrix-based samples. This discrepancy can be examined by scrutinizing the data declared in the validation report on matrix interference studies and conducting an audit of routine quality samples that pertain to these components, including matrix blanks and spike replicates.

Detector Manipulation

Audit Deliverable Purpose: To investigate the manipulation of detector settings, which may allow interfering compounds to be mis-integrated as target compounds.

Recommended Audit Actions: Audit instrument detector settings, emphasizing UV or visible light frequency, the quantitation versus qualifier detector channels, and any qualifying channel ratios derived from analytical standards. This audit will focus on known interferences declared in the analytical method's validation report and the probability of these interferences having a substantive impact on the final reported result of the target compound.

Data Analysis Manipulation

Audit Deliverable Purpose: To investigate the manipulation of data analysis procedure, emphasizing the mis-integration of target compounds, mis-integration, and manipulation of calibration standard integration.

Recommended Audit Actions: Conduct an audit of instrument chromatogram integration procedures, policies, and practices involving a comprehensive review of all manually integrated peaks from a randomly selected analytical batch conducted by the laboratory. The investigation will collect data on the amount and frequency of manual integrations versus auto-integrations per analytical batch for baseline consistency from peak to peak and the relationship of integration technique between calibration, quality, and client samples.

Physical Instrument Parameter Manipulation

Audit Deliverable Purpose: To investigate the alteration of physical parameters on the analytical instrument, which could be altered from the values on the analytical method's validation report and the method as performed during a Proficiency Testing (PT) round, by tracking the logs that would show a lack of manipulation of these physical variables, the presence of alterations suggesting manipulation, or missing segments of data that may or may not coincide with periods of high reported values by the laboratory.

Recommended Audit Actions: Audit all instrument logs that verify the invariance of physical variable settings that impact the final reported value. These include injector volumes, flow rates, temperature settings, vacuum pressures, electrovoltaic parameters, and electromagnetic parameters (mass spec methodologies only). Traceability practices showing the physical parameters of the analytical method printed into each data packet by each analytical batch would make a step of the audit performable with document and data review only. If the laboratory in question does not adhere to standard traceability practices, on-site audits of current and established procedures will be essential to validate the uniformity of these physical instrument parameters.

Appendix 3: Outline of General QMS Analysis Laboratory Audit Elements

We have outlined general guidelines for method validation and QMS data management for cannabis analysis laboratories to show the legal defensibility of all reported data and maintain the quality logs that help support and prove these assertions.

We have outlined the stages here below:

	Criteria			
	Required		**Ideal**	
1. **Linearity and LOQ derivation**				
1.A Calibration 1-n	R^2>0.99, >5 Cal Points		>7 Cal Points	
1.B Replicate Injections (7+)	LOQ < Action Level		LOQ < AL/5	
2. **Matrix Spike Recovery Replicates**	Accuracy	Precision	Accuracy	Precision
2.A Flower	±30%	±0.30	±20%	±0.15
2.B Concentrate	±30%	±0.30	±20%	±0.15
2.C Edibles01	±30%	±0.30	±20%	±0.15
2.D Edibles02 (if applicable)	±30%	±0.30	±20%	±0.15
3. **Robustness and LQC**				
Matrix QC:				
PB and MB	<LOQ		<LOD	
LCS	70-130% Recovery		80-120% Rec.	

LRS	<30% RPD	<30% RPD
ICV	70-130% Recovery	80-120% Rec.
Matrix CRM	70-130% Recovery	80-120% Rec.
CCV	70-130% Recovery	80-120% Rec.
CCB	<LOQ	<LOD

Matrix-Specific Sample Classes for Validation and Per-Batch Sample Prep

Flower – Cannabis flower or proxy (hemp bud, hops bud, etc)

Concentrate – Organic hemp oil

Edibles01 Hydrophilic – Gummy bears

Edibles02 Hydrophobic – Chocolate bars

QMS On-Going Per-Batch Requirements

ICV	Independent Calibration Verification	±30% recovery
PB	Prep Blank	<LOQ
MB	Matrix Blank	<LOQ
MS	Matrix Spike	±30% recovery
SD	Sample Duplicate	<30% RPD
CRM	Matrix CRM “Unknown”	±30% recovery
CCV	Continuing Calibration Verification	±30% recovery
CCB	Continuing Calibration Blank	<LOQ

SINGLE CALIBRATION		
Sample Text	**Matrix**	**QC**
Calibration 01	Solvent	Calibration
Calibration 02	Solvent	Calibration
Calibration 03	Solvent	Calibration
Calibration 04	Solvent	Calibration
Calibration 05	Solvent	Calibration
Calibration 06	Solvent	Calibration
Calibration 07	Solvent	Calibration
Calibration 08	Solvent	Calibration
Internal Calibration Verification	Solvent	ICV
Prep Blank	Solvent	PB
Matrix Blank	Flower	MB
Matrix Spike	Flower	LCS or MS
Sample Duplicate	Flower	SD or MR
Flower Samples	Flower	S01-S10
Continuing Calibration Verification	Solvent	CCV
Continuing Calibration Blank	Solvent	CCB
Matrix Blank	Concentrate	MB
Matrix Spike	Concentrate	LCS or MS
Sample Duplicate	Concentrate	SD or MR
Flower Samples	Concentrate	S11-S20
Continuing Calibration Verification	Solvent	CCV
Continuing Calibration Blank	Solvent	CCB
Matrix Blank	Other	MB
Matrix Spike	Other	LCS or MS
Sample Duplicate	Other	SD or MR
Flower Samples	Other	S21-S30
Continuing Calibration Verification	Solvent	CCV
Continuing Calibration Blank	Solvent	CCB

TOTAL RUNS SINGLE CAL ^	**28**
TOTAL RUNS MATRIX CAL >	**48**

LEGEND

Solvent	
Flower Samples	
Concentrate	
Other	

MATRIX CALIBRATION		
Sample Text	**Matrix**	**QC**
Calibration 01	Flower	Calibration
Calibration 02	Flower	Calibration
Calibration 03	Flower	Calibration
Calibration 04	Flower	Calibration
Calibration 05	Flower	Calibration
Calibration 06	Flower	Calibration
Calibration 07	Flower	Calibration
Calibration 08	Flower	Calibration
Internal Calibration Verification	Flower	ICV
Prep Blank	Flower	PB
Matrix Blank	Flower	MB
Matrix Spike	Flower	LCS or MS
Sample Duplicate	Flower	SD or MR
Flower Samples	Flower	S01-S10
Continuing Calibration Verification	Flower	CCV
Continuing Calibration Blank	Flower	CCB
Calibration 01	Concentrate	Calibration
Calibration 02	Concentrate	Calibration
Calibration 03	Concentrate	Calibration
Calibration 04	Concentrate	Calibration
Calibration 05	Concentrate	Calibration
Calibration 06	Concentrate	Calibration
Calibration 07	Concentrate	Calibration
Calibration 08	Concentrate	Calibration
Internal Calibration Verification	Concentrate	ICV
Prep Blank	Concentrate	PB
Matrix Blank	Concentrate	MB
Matrix Spike	Concentrate	LCS or MS
Sample Duplicate	Concentrate	SD or MR
Flower Samples	Concentrate	S01-S10
Continuing Calibration Verification	Concentrate	CCV
Continuing Calibration Blank	Concentrate	CCB
Calibration 01	Other	Calibration
Calibration 02	Other	Calibration
Calibration 03	Other	Calibration
Calibration 04	Other	Calibration
Calibration 05	Other	Calibration
Calibration 06	Other	Calibration
Calibration 07	Other	Calibration
Calibration 08	Other	Calibration
Internal Calibration Verification	Other	ICV
Prep Blank	Other	PB
Matrix Blank	Other	MB
Matrix Spike	Other	LCS or MS
Sample Duplicate	Other	SD or MR
Flower Samples	Other	S01-S10
Continuing Calibration Verification	Other	CCV
Continuing Calibration Blank	Other	CCB

Chart 08: Matrix-matched LQC v. Matrix-matched calibration and batch preparation. All LQCs are indicated with the acronym used in the preceding section.

The below image, **Chart08** line, illustrates each analysis performed by the laboratory for a

full-compliance suite of testing for a state-regulated COA. Water activity, foreign matter, and moisture are required but not shown.

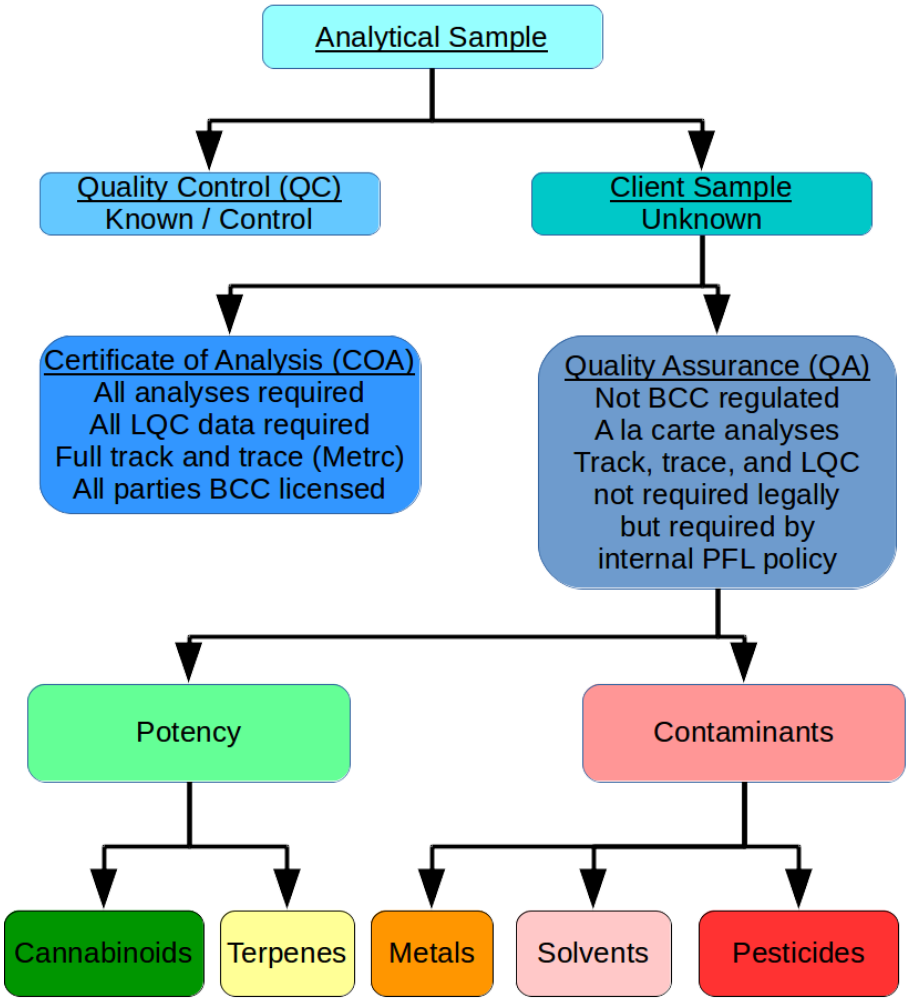


Chart 09: Flow Diagram of Analytical Samples that may be submitted to the lab. Colors match the instrument color-coded diagrams and labels.

As shown in **Chart 08** and **Chart 09**, the LQC samples associated with a batch of client samples must pass their criteria for the client sample data to be considered valid. It will be imperative if regulators or accreditation under ISO perform an audit or if a former client attempts legal action against the lab. The LQC data associated with the client data is the main form of

defense that will be at the lab's disposal.

Standard LQC Set (per each matrix class)		
ACRONYM	**Full LQC Name**	**Criteria**
PB	Prep Blank	<LOQ
MB	Matrix Blank	<LOQ
LCS	Lab Control Standard	70-130%
LRS	Lab Replicate Sample	<30% RPD
ICV	Independent Cal Verification	70-130%
CCV	Continuing Calibration Verification	70-130%
CCB	Continuing Calibration Blank	<LOQ

Chart 10: Chart summarizing the LQC requirements of the cannabinoid analysis method. Except for microbiology, moisture content, water activity, and foreign matter analysis, all other analyses will have the same LQC criteria.

The logical flow of the LQC samples and the logical tests that their status as “PASS” or “FAIL” prove (or disprove) can best be summarized in a flow chart with critical decision points in the protocol or process done by the analyst outlined in a simple binary yes/no schematic. This flow chart is essentially a reproduction or is redundant with the SOP of the analytical method, especially the LQC section of the protocol. When the flow chart is followed correctly, the laboratory will generate and record all necessary LQC for compliance and legal protection of the lab. Following this chart will ensure that all necessary LQC samples are prepared and run at the instrument by the preparation technician in the laboratory. This flow chart does not address how to analyze the data generated by the LQC samples to qualify the accuracy of the client samples. That topic is addressed in the following paragraphs.

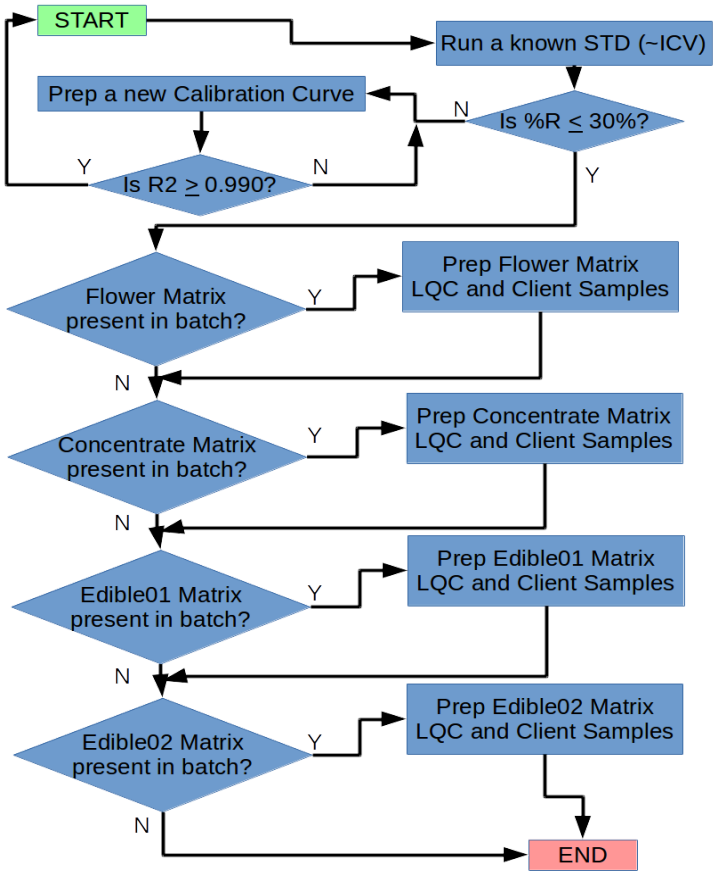


Chart 11: Flow chart of decisions of LQC samples. The diagram is designed to be started on the top left in the green box labeled “START” and flows through a series of yes/no decision points labeled Y and N for yes and no, respectively. The flowchart ends with the red box in the lower right corner labeled “END.” Diamond-shaped boxes represent binary decision points (yes/no), and rectangles represent steps or procedures to be carried out.

Below is a series of sample LQC batch data summarized as either “PASS” or “FAIL” and color-coded appropriately (with green and red, respectively).

Contaminated Consumables		
PB	Prep Blank	FAIL
MB	Matrix Blank	FAIL
LCS	Lab Control Standard	PASS
LRS	Lab Replicate Sample	PASS
ICV	Independent Cal Verification	PASS
CCV	Continuing Calibration Verification	PASS
CCB	Continuing Calibration Blank	FAIL

Chart 12: Sample LQC Data and Associated Possible Diagnosis - Contaminated Consumables

If multiple blanks show contamination, then it is likely that some component in the sample prep process is contaminating all of the samples (or many of them) in the analytical batch. Positive controls, such as the LCS, may have larger expected values, so the contamination may not be visible or shown in the available statistics.

Contaminated Matrix Proxy (Minor)		
PB	Prep Blank	PASS
MB	Matrix Blank	FAIL
LCS	Lab Control Standard	PASS
LRS	Lab Replicate Sample	PASS
ICV	Independent Cal Verification	PASS
CCV	Continuing Calibration Verification	PASS
CCB	Continuing Calibration Blank	PASS

Chart 13: Sample LQC Data and Associated Possible Diagnosis – Contaminated Matrix Proxy (Minor)

If only one blank fails, and it is the Matrix Blank (MB), the matrix proxy used to prepare the LQC may either be contaminated or exhibiting an interference-based false positive. Switching the MB to a new material as a diagnostic tool in identifying the source of contamination is a natural next step.

Contaminated Matrix Proxy (Major)		
PB	Prep Blank	PASS
MB	Matrix Blank	FAIL
LCS	Lab Control Standard	FAIL
LRS	Lab Replicate Sample	PASS
ICV	Independent Cal Verification	PASS
CCV	Continuing Calibration Verification	PASS
CCB	Continuing Calibration Blank	PASS

Chart 14: Sample LQC Data and Associated Possible Diagnosis – Contaminated Matrix Proxy (Major)

If both the Matrix Blank (MB) fails and laboratory Control STD (LCS) fails, the matrix proxy

may be so contaminated that it is interfering with %R of the LCS. It is a sign of more significant contamination than what was outlined in .

Instrument Carry-Over		
PB	Prep Blank	FAIL
MB	Matrix Blank	FAIL
LCS	Lab Control Standard	PASS
LRS	Lab Replicate Sample	PASS
ICV	Independent Cal Verification	PASS
CCV	Continuing Calibration Verification	PASS
CCB	Continuing Calibration Blank	FAIL

Chart 15: Sample LQC Data and Associated Possible Diagnosis – Instrument Carry-Over

If all blanks fail, but all positive controls pass, the contamination may not be from sample prep and consumables but from instrument carry-over between runs. It means the method needs to be modified to allow for a more thorough purging of analytes between analytical sample runs. It can be verified with a null injection (tray position = -1), which performs an analytical run without injecting a volume of the analytical sample from the vial. If the null injection is contaminated, then that confirms that the instrument carry-over is the issue causing the LQC failures.

Instrument Mis-Calibration		
PB	Prep Blank	PASS
MB	Matrix Blank	PASS
LCS	Lab Control Standard	FAIL
LRS	Lab Replicate Sample	PASS
ICV	Independent Cal Verification	FAIL
CCV	Continuing Calibration Verification	FAIL
CCB	Continuing Calibration Blank	PASS

Chart 16: Sample LQC Data and Associated Possible Diagnosis – Instrument Mis-Calibration

If the blanks are all passing, and the LRS is passing, but all other positive controls are failing, then the issue is miscalibration. It can be fixed by re-running existing calibration dilutions, and if the problem persists, preparing a fresh calibration curve from a stock solution will cure it. Check the R^2 of the calibration curves after re-running the calibration dilutions to verify the calibration is BCC or equivalent state regulator compliant.

Instrument Drift (Detector Stability) [Major]		
PB	Prep Blank	PASS
MB	Matrix Blank	PASS
LCS	Lab Control Standard	FAIL
LRS	Lab Replicate Sample	FAIL
ICV	Independent Cal Verification	FAIL
CCV	Continuing Calibration Verification	FAIL
CCB	Continuing Calibration Blank	PASS

Chart 17: Sample LQC Data and Associated Possible Diagnosis – Instrument Drift (Detector Stability) [Major]

If blanks pass but all positives, including CCVs, are failing, then it is likely that in addition to a possible miscalibration, there may also be instrument drift. The sole distinction between these concepts lies in their continuity: a miscalibration could be a consistent and replicable process that is not accurately centered on the most precise result. Conversely, a detector drift might initiate with a perfect calibration at the commencement of the analytical batch but drift so rapidly in response that subsequent samples in the batch fall outside the acceptance window of compliance criteria.

Instrument Drift (Detector Stability) [Minor]		
PB	Prep Blank	PASS
MB	Matrix Blank	PASS
LCS	Lab Control Standard	PASS
LRS	Lab Replicate Sample	FAIL
ICV	Independent Cal Verification	PASS
CCV	Continuing Calibration Verification	FAIL
CCB	Continuing Calibration Blank	PASS

Chart 18: Sample LQC Data and Associated Possible Diagnosis - Instrument Drift (Detector Stability) [Minor]

Sometimes, the instrument drift is very subtle and does not cause all positive controls (such as the LCS) to fall outside of the acceptance criteria. However, it is still essential to diagnose instrument detector drift as it is one of the primary causes of batch failure, particularly late or end-of-batch CCVs. The LRS can sometimes detect drift the earliest because it analyzes two identical injections and measures their deviation. If this number is very high, even if all other LQCs pass, there is still significant instrument drift.

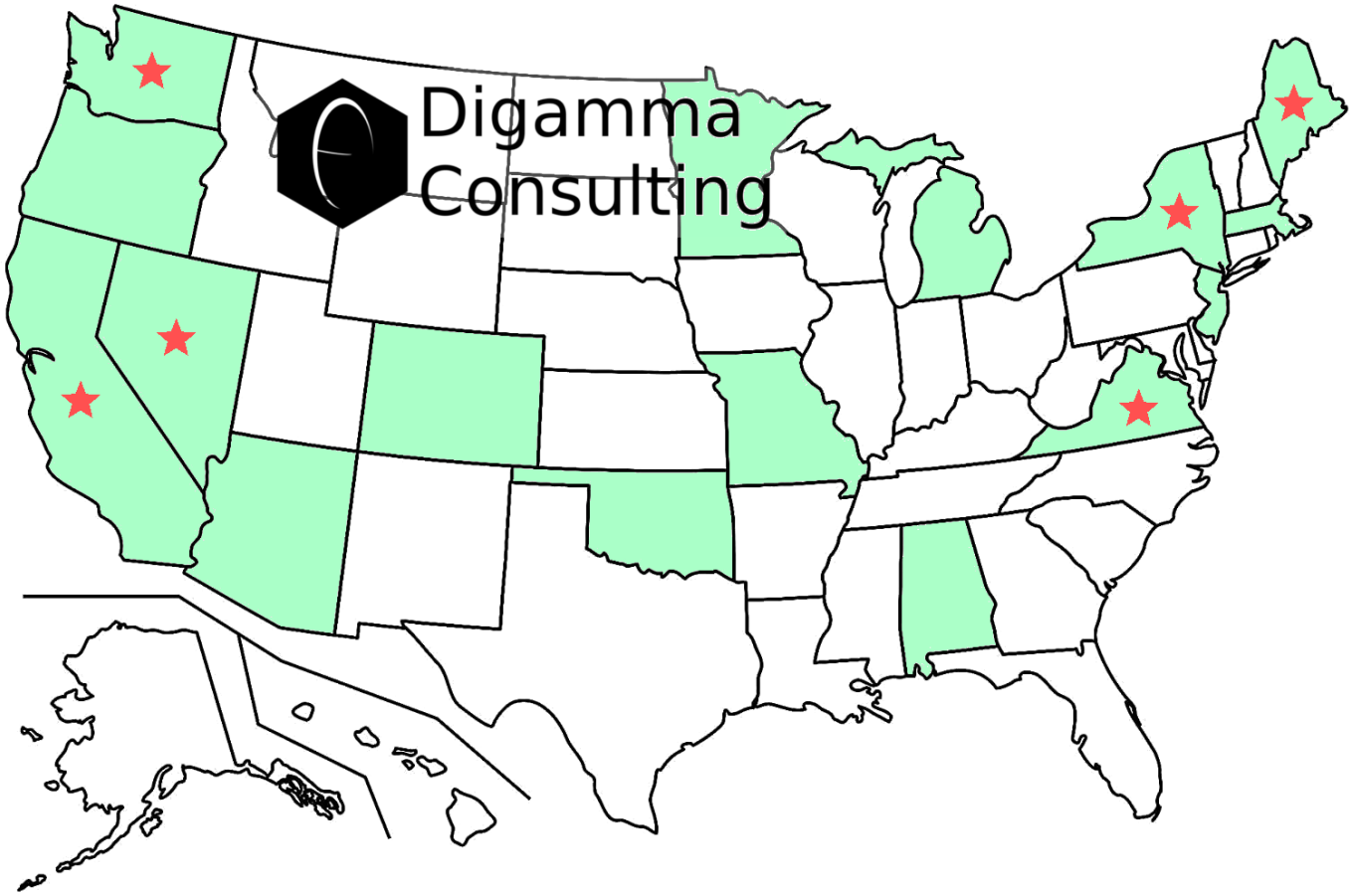
Expired Standards (CAL or ICV or both)		
PB	Prep Blank	PASS
MB	Matrix Blank	PASS
LCS	Lab Control Standard	PASS
LRS	Lab Replicate Sample	PASS
ICV	Independent Cal Verification	FAIL
CCV	Continuing Calibration Verification	PASS
CCB	Continuing Calibration Blank	PASS

Chart 19: Sample LQC Data and Associated Possible Diagnosis – Expired Standards (CAL or ICV or both)

If all LQCs pass except for the ICV, then the issue may be that the standards the analyst is working with are expired and no longer valid. Even if the standard is not expired, improper storage conditions, which may not be visible or detected by the analyst using the standard, could also cause the accuracy of the calibration to falter. If this issue occurs, re-prepping all calibration and ICV standards from fresh stock solutions generally resolves the problem. If time and resources permit, a small diagnostic experiment can be performed to track the source of the error, allowing it to be noted in the lab's QMS error logs and allowing future edits and changes to methodologies to avoid or minimize those errors.

Appendix 4: Digamma Company *Cirriculum Vitae* and Experience

Digamma's typical clients include start-up cannabis analysis labs in 16 states and 4 countries, including New Zealand, Germany, Pakistan, and the United States. We have shown a map representing our licensed clients below:



An outline of the consulting projects successfully performed by Digamma Consulting, totaling over 45 laboratories. Digamma Consulting performs validations on chemical processes and drafts, edits, and submits laboratory validation reports (analytical) or applications (manufacturing) to regulatory bodies needed for state license application. If other services were performed they are indicated below.

ACTION	COMPANY	LOCATION	START	END	TASK
Founding	Digamma	Oakland, CA	2013/12/01	Present	Creating Initial Company Names, Data Systems, Marketing Material, Etc
Product Development	Flow Kana	Oakland, CA	2014/03/15	2014/03/16	Consulting for regulations in the cannabis industry
Analytical Laboratory Installation	Cannabinology	San Rafael, CA	2016/12/05	2018/03/26	Installation of Analytical Laboratory: Cannabinoids, Terpenes, Solvents, Pesticides, Metals
Incorporation	Digamma	Oakland, CA	2017/01/01	Present	Creating Initial Bank Account, Fictitious Name State, Filing Incorporation and Tax Documents
Analytical Laboratory Installation	Guild Extracts	Oakland, CA	2017/04/03	2018/12/05	Consulting for THC product start up
Analytical Laboratory Installation	Bel Costa Labs	Long Beach, CA	2017/06/16	2019/10/07	Installation of Analytical Laboratory: Cannabinoids, Terpenes, Pesticides, Metals
Analytical Laboratory Installation	Forensic Analytical Laboratories	Hayward, CA	2017/07/03	2018/08/14	Installation of Analytical Laboratory: Solvents
Product Development	Bend Solutions Group	Bend, OR	2017/07/27	2017/08/08	Consulting for CBD product start up
Product Development	CB Therapeutics	San Diego, CA	2017/08/09	2018/01/30	Consulting for synthetic cannabinoid synthesis start up
Product Development	Arya	Denver, CO	2017/08/09	2017/09/08	Consulting for CBD product start up
Product Development	TruCBD	Bend, OR	2017/08/11	2017/09/18	Consulting for CBD product start up
Product Development	Phil Borghuis	Corte Madre, CA	2017/10/19	2017/10/24	Consulting for CBD product start up
Product Development	Purple Queen Production	Las Vegas, NV	2017/10/20	2017/10/24	Consulting for CBD product start up
Application Consultation	Higher Yields Consulting	Denver, CO	2017/11/08	2019/09/28	Consulting for cannabis state licensing applications
Product Development	Divine Alchemy	San Francisco, CA	2017/11/12	2017/12/28	Consulting for vape start up
Product Development	Flowerpilot	Berlin, Germany	2017/11/17	2018/08/06	Consulting for novel instrument development
Analytical Laboratory Installation	Pure Analytics	Santa Rosa, CA	2017/12/18	2018/01/21	Installation of Analytical Laboratory: Pesticides
Product Development	Kin Slips	Oakland, CA	2018/02/26	2018/10/12	Consulting for THC product start up
Analytical Laboratory Installation	Encore Labs	Pasadena, CA	2018/03/03	2018/04/27	Installation of Analytical Laboratory: Pesticides

ACTION	COMPANY	LOCATION	START	END	TASK
Product Development	Om Edibles	Berkeley, CA	2018/03/04	2018/06/08	Consulting for THC product start up
Analytical Laboratory Installation	Health Liberty Products	Nelson, New Zealand	2018/04/29	2019/06/19	Installation of Analytical Laboratory: Cannabinoids
Data Consulting	Emerald Scientific	San Luis Obispo, CA	2018/04/29	2020/10/19	Consulting for data analysis and data reporting
Analytical Laboratory Installation	BioCann Labs	Irvine, CA	2018/09/25	2020/05/04	Installation of Analytical Laboratory: Cannabinoids, Terpenes, Solvents
Analytical Laboratory Installation	Movad Labs	Los Angeles, CA	2018/10/05	2020/04/26	Installation of Analytical Laboratory: Cannabinoids, Terpenes, Solvents, Pesticides, Metals
Court Witness	Michael Cindrich	San Diego, CA	2019/01/03	2020/03/01	Consulting as scientific expert witness for legal trials
Methodology Documents	Green Country Scientific	Tulsa, OK	2019/01/24	2019/04/05	Licensing of Analytical Methodology Procedure Documentation
Analytical Laboratory Installation	Evio	Berkeley, CA	2019/02/11	2019/02/25	Installation of Analytical Laboratory: Pesticides
Methodology Documents	Apricot Analytics	Oakland, CA	2019/05/16	2019/06/19	Licensing of Analytical Methodology Procedure Documentation
Analytical Laboratory Installation	EcoGen Labs	Grand Junction, CO	2019/06/11	2019/06/14	Installation of Analytical Laboratory: Cannabinoids
Analytical Laboratory Installation	NatureSafe Labs	San Diego, CA	2019/09/02	2020/09/02	Installation of Analytical Laboratory: Cannabinoids, Terpenes, Solvents, Pesticides, Metals
Analytical Laboratory Installation	Verity Analytics	San Diego, CA	2019/09/10	2020/01/08	Installation of Analytical Laboratory: Cannabinoids, Terpenes, Solvents, Pesticides, Metals
Analytical Laboratory Installation	ACT Labs	Lansing, MI	2020/01/07	2020/02/25	Installation of Analytical Laboratory: Solvents, Pesticides
Analytical Laboratory Installation	ProForma Labs	Salinas, CA	2020/06/08	2021/02/22	Installation of Analytical Laboratory: Cannabinoids, Terpenes, Solvents, Pesticides, Metals
Analytical Laboratory Installation	Cloud TEN	Saint Louis, MO	2021/02/05	2021/08/31	Installation of Analytical Laboratory: Cannabinoids, Terpenes, Solvents, Pesticides, Metals
Analytical Laboratory Installation	Green Precision Anaytics	Kansas City, MO	2021/04/26	2021/09/14	Installation of Analytical Laboratory: Solvents

ACTION	COMPANY	LOCATION	START	END	TASK
Manufacturing Facility SOPs and application	LexiCann NJ	Jersey City, NJ	2021/11/07	2021/12/14	Authoring of Quality and Operations Manual
Manufacturing Facility SOPs and application	Harvest Works Farms	Molmdel, NJ	2021/10/26	2021/12/14	Authoring of Quality and Operations Manual
Legislative Consultation	Oneida Indian Nation	Oneida, NY	2022/03/04	2022/03/25	Consulting on Legislation for a Sovereign Indian Nation acting as a State Government
Analytical Laboratory Installation	ATC Labs	Scarsdale, AZ	2022/04/13	2022/06/21	Installation of Analytical Laboratory: Solvents, Pesticides, Terpenes
Analytical Laboratory Installation	Steadfast Lab	Hazel Park, MI	2022/05/13	2022/05/16	Authoring of Standard Operating Procedures for Pesticides
Analytical Laboratory Installation	Bloomfield Hills, MI	Warren, MI	2022/04/13	2022/06/21	Authoring of Standard Operating Procedures for Solvents
Analytical Laboratory Installation	CATLAB	Kittery, ME	2022/06/06	2022/06/22	Installation of Analytical Laboratory: Solvents
Analytical Laboratory Installation	Green Precision Anaytics	Kansas City, MO	2022/07/25	2022/08/05	Installation of Analytical Laboratory: Cannabinoids and Terpenes
Analytical Laboratory Installation	Green Precision Anaytics	Kansas City, MO	22/10/09	2022/11/04	Installation of Analytical Laboratory: Pesticides
Manufacturing Facility SOPs and application	Evexia	Tuscaloosa, AL	11/07/22	12/20/22	Authoring of Quality and Operations Manual
Analytical Laboratory Installation	Phyto-Farma Labs	Warwick, NY	03/03/23	04/04/23	Installation of Analytical Laboratory: Microbiology
Analytical Laboratory Installation	Mille Lacs Corporate Ventures	Onamia, MN	03/07/23	04/12/23	Installation of Analytical Laboratory: Lab-Wide Cost Benefit Analysis

Whitepaper

Digamma Consulting

The Federal Recreational Hemp Phenomenon

By Marco Troiani

The purpose of this document is to outline the draft of the federal recreational hemp phenomenon, including each sub-section. The document itself begins in the first section, but this paragraph is intended as an orienting text to help guide a reader through the draft and its component sections with ease.

EMERALD SCIENTIFIC

HISTORY

Many people know cannabis as an illicit and popular recreational drug from their youth. As many young people are prone to questioning established traditions, the contrast between the legality, and social harm, of alcohol and the illegality of cannabis may have raised some eyebrows. Alcohol was legal but was associated with violence and anti-social behavior, but cannabis was associated with peaceful hippies and dropouts. Additionally, the toxicity of alcohol, especially over a long period of time, was starting to be known to the general public, and evidence was starting to show that cannabis lacked the highly toxic profile of alcohol. At the close of the 20th century, many were thinking that the legalization of cannabis was a phenomenon to be experienced in their lifetime.

Starting at the end of the 20th century, cannabis began being decriminalized and legalized by U.S. state governments, starting with medical cannabis in California in 1996 thanks to the Dennis Peron-driven proposition 215, which was borne out of the HIV/AIDS crisis in the gay community, primarily centered on San Francisco's Castro neighborhood. Since those days in 1980s, a large amount of peer-reviewed medical science papers have come out showing that cannabinoids and terpenoids present in cannabis helped to treat AIDS symptoms, such as AIDS-associated wasting syndrome. This effectiveness was so astounding during the medical crisis caused by HIV/AIDS that, even with a federal prohibition on cannabis, a THC pharmaceutical formulation was approved by the FDA for HIV/AIDS wasting syndrome and it was marketed under the name Marinol, with the generic name Dronabinol.

After California had established that medical cannabis programs initiated by state legislation chambers were possible, more states began to follow in the legalization process. Although federal officers continued to enforce federal cannabis prohibition on operators that were legal in the eyes of the state of California, state authority to legalize cannabis for medical purposes had been established. In 2012, both Colorado and Washington passed recreational adult-use bills that lifted the medical necessity as a prerequisite to cannabis consumption.

The introduction of recreational (sometimes called adult-use) bills expanded the profitability of cannabis significantly. At the time, California's medical program was only allowing medically relevant exceptions to federal laws, which only affect a small portion of the population. Even within this population, only a minority of eligible patients would use cannabis, as many were wary of the illicit association. The Colorado and Washington recreational bills demonstrated to the United States generally that a lucrative market was possible in nearly every U.S. state. In the years after 2012, some financial thinkers in the U.S. were stating that the national legalization and taxation of cannabis would be capable of balancing the debt on the federal or state budget.

As various waves of legalization worked through various states at the medical and recreational level, the so-called green wave seemed to be in full effect. As of April 2023, 22 states, two territories, and Washington, DC all had some form of cannabis legalization. Dispensaries open to anyone aged 21 and over, previously a phenomenon associated with Denver, CO, can now be seen all over the west coast, in about half of the east coast states, and also in mid-western states like Michigan and Missouri.

But as more states initiated cannabis programs, the federal prohibition on cannabis remained on the books, if not fully enforced. After 2013, U.S. Deputy Attorney General James M. Cole issued the Cole Memorandum, instructing federal prosecutors not to use federal resources to enforce federal cannabis prohibition in a state where it had been legalized by the state government. This brought an end to the threat of federal agents taking action against state-licensed cannabis operators, but many of the federal restrictions still prevented the cannabis industry from growing organically. All interstate commerce is prohibited for the cannabis industry as that is well defined as federal jurisdiction. This has created an economic landscape where cannabis operators re-apply as a new entity in new jurisdictions rather than simply directly expanding as traditional business would. Financial and tax issues surrounding the 280E clause that prevents cannabis business from writing off the Cost of Goods Sold (COGS) when those goods are Schedule I substances also severely limits the profitability of state-licensed cannabis business when compared to similar industries.

As the legal cannabis market seemed to stabilize leading up to 2018, a new phenomenon started appearing in the U.S. CBD products were being sold not only in state-licensed dispensaries but were showing up in nearly every corner smoke

shop in the country, regardless of whether that state had passed a cannabis reform bill or not. These CBD products were not produced from state-licensed cannabis but from federally legal hemp. These products were being distributed to low cost and ubiquitous vendors all over the country and without taking the 280E tax penalty that state-licensed operators were bound to. There seemed to be a federal loophole for cannabinoids derived from hemp to bypass the ills of the state-licensed operators, but it appeared to only apply to the non-psychoactive compound CBD.

As this federal cannabinoid loophole became more well known, psychoactive cannabinoids started appearing in smoke shops all over the country as well. Delta-8-THC and hexahydrocannabinol (HHC) are two of the more popular examples sold as edibles and vape pens in many smoke shops. When the federal hemp law that was originally designed for industrial hemp started applying to medically relevant cannabinoids like CBD, it seemed a reasonable state of affairs due to CBD's non-psychoactive status and low potential for abuse. CBD from hemp seemed more similar to a vitamin or supplement taken for a consumer's wellbeing than a recreational drug. But when the psychoactive cannabinoids began to appear on a less regulated market, a different landscape emerged. What many state-licensed operators that produce completely natural psychoactive cannabis are finding is that they are in unfair competition with recreational hemp operators. Some consumers are starting to prefer these more common and reliable brands that are present all over the country over the patchwork of competing state-level operators that run local dispensaries.

At this time, the recreational cannabinoid market seems to be upside down thanks to the explosion of the recreational hemp phenomenon. To better understand this phenomenon and the practical consequences of it for the industry, the technical aspects have been organized into the three categories of chemistry: law, analysis, and a brief conclusion. Because different readers have different areas of expertise and in-depth knowledge, the division is designed to assist each reader in finding the most relevant and helpful information.

CHEMISTRY

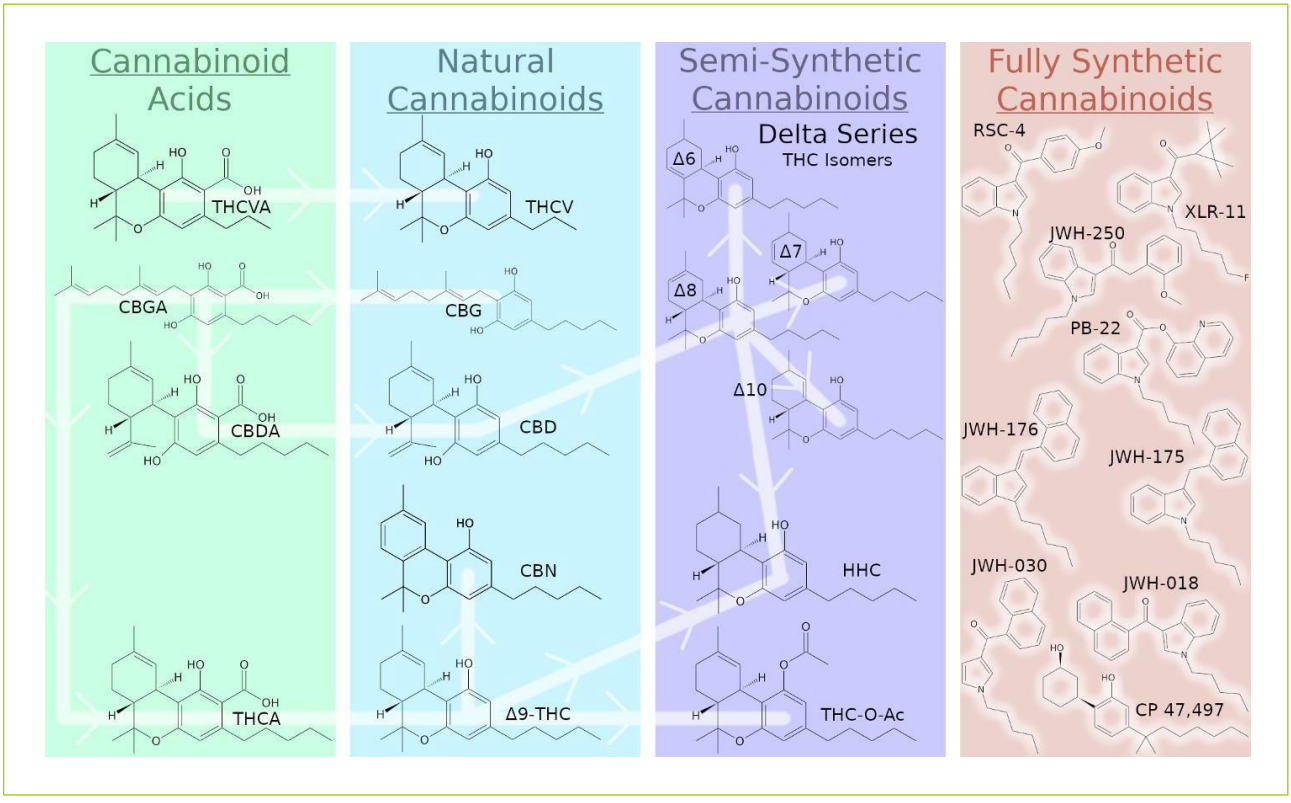
To properly understand the history, law, and future opportunities relating to cannabinoid compounds, familiarity with the chemistry of these compounds is critical. A scope has been presented here that is deep enough for a professional chemist, but broad and clear enough to be helpful to non-scientists to whom this information has relevant consequences.

Cannabinoid chemistry can appear both complex in nature and vast in scope, so an illustrative diagram outlining the chemistry has been created in Imageα below. The image has four parallel columns categorizing cannabinoid compounds from left-to-right: natural cannabinoid acids, natural cannabinoid neutrals, semi-synthetic cannabinoids, and fully synthetic cannabinoids.

Cannabinoid acids are the compounds produced by the cannabis plant. These organic acids are generally precursors to the more familiar cannabinoids included in the next section, natural cannabinoids, such as THC and CBD. Their acid forms, THCA and CBDA, respectively, are the compounds actually produced by the plant itself.

Natural cannabinoid neutrals are created from cannabinoid acids by natural physical processes. Most involve decarboxylation, a process that converts acids to their free cannabinoid forms, releasing carbon dioxide (such as THCA → THC or CBDA →CBD). This process happens spontaneously at the high temperatures associated with smoking and baking, and much more slowly at room temperature in the presence of excess light.

Semi-synthetic cannabinoids are those that are synthesized from natural cannabinoids through a man-made chemical reaction. These can include



Imageα – An illustrative diagram showing the chemical structure of the four major classes of cannabinoids: cannabinoid acids (green), natural cannabinoids (blue), semi-synthetic cannabinoids (purple), and fully synthetic cannabinoids (red). The sources of each molecule are related to other molecules in the diagram through white arrows indicating a chemical reaction. Image credit: Digamma.

compounds such as THC-O-Acetate, HHC, and the delta series of THC isomers, such as delta-8-THC.

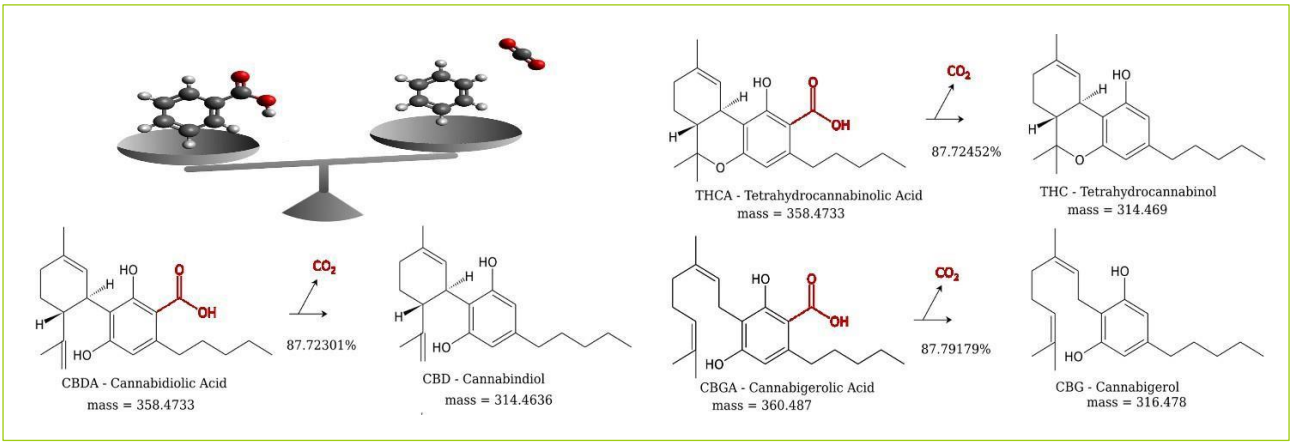
Fully synthetic cannabinoids are compounds that are synthesized in a laboratory by precursor chemicals that bear little structural similarity to natural cannabinoids but are known to activate biochemical cannabinoid receptors. The term phytocannabinoid (meaning from a plant source) is used to distinguish from both synthetic cannabinoids and animal-derived endocannabinoids such as anandamide.

To help illustrate the transitions from cannabinoid acid to free cannabinoid, we have reproduced a decarboxylation diagram in Image**β**. The top-left image shows how the loss of the carboxyl group as CO^2 leaves less mass of substance after decarboxylation, a loss that can affect the final yield calculations of any end product. The remaining quadrants show the exact mass loss for the three most common cannabinoid acids: THCA, CBGA, and CBDA. To help make these mass losses more intuitive, we have displayed the remaining mass, after decarboxylation, as a percentage of the original mass, for each cannabinoid decarboxylation reaction.

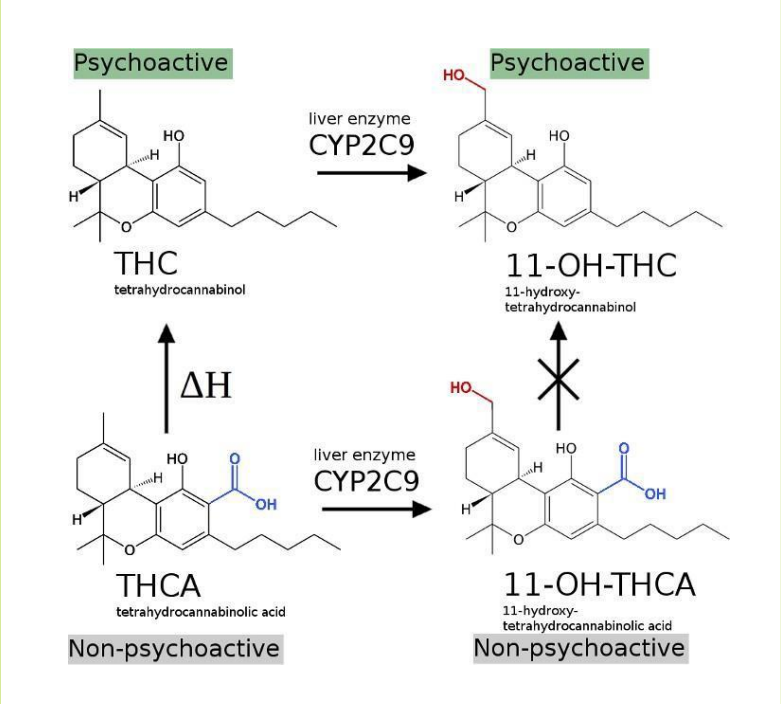
There are medically relevant differences between cannabinoids and cannabinoid acids, too. Until recently, many cannabis producers incorrectly assumed that because THCA converts to THC so readily outside the human body that ingested THCA would become THC in the human body. What experiments have shown is that once THCA enters the human body it will not convert to THC or its metabolites in any appreciable amount. Interestingly, both THCA and THC are metabolized by the same liver enzyme (CYP2C9), but inter-conversion after ingestion is not believed possible at this time. The lack of inter-conversion has particularly salient consequences when one considers that THCA isomers tend to be non-psychoactive whereas THC isomers tend to be psychoactive in humans. We have illustrated this phenomenon in Image**γ**.

To cover the remaining chemical phenomenon that are relevant to understanding the recreational hemp phenomenon, it may be helpful to look back to the year 2014. At this point in time, Colorado has recreational cannabis, but California, Maine, Massachusetts, and Nevada still have medical cannabis programs that are poised to expand to recreational in all four states in November 2016; the 2018 Farm Bill was still years away, and CBD was being treated as a non-psychoactive unregulated supplement with a high cost.

In 2014, many farmers were looking at hemp as a new opportunity to sell unscheduled drugs such



Imageβ – An image showing the concept of decarboxylation with an emphasis on cannabinoids. Clockwise from top-left: an illustration of how the loss of a carboxylic acid through decarboxylation causes a loss of mass (weight), a skeletal diagram showing the exact mass of decarboxylation of THCA>THC, a skeletal diagram showing the exact mass of decarboxylation of CBGA>CBG, a skeletal diagram showing the exact mass of decarboxylation of CBDA>CBD. Image credit: Digamma.

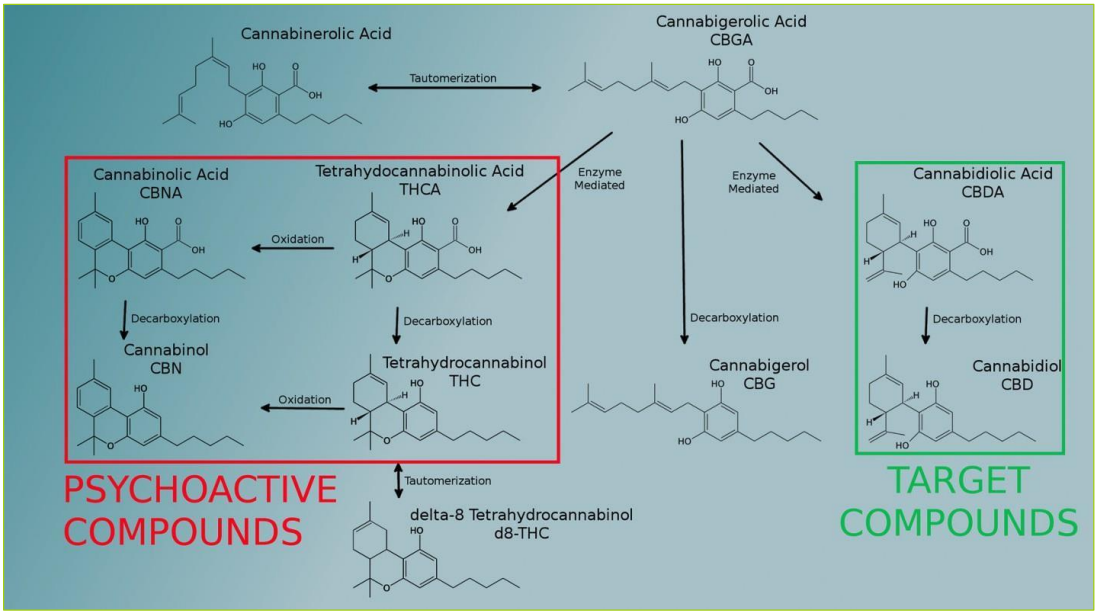


Imageγ – A diagram outlining the biochemically and medically relevant aspects of cannabinoid v. cannabinoid acid metabolism. The precursor THCA is present in the bottom-left of the image, showing the heat mediated decarboxylation creating THC in the top-left. Both THCA and THC are metabolized by CYP2C9 (liver enzyme) to create the 11-OH metabolites of both components. The psycho-activity of each of these components and their natural human metabolites is indicated with green/gray text. Image credit: Digamma.

as CBD. In setting up such a cultivation facility, prospective hemp farmers were concerned about the psychoactive substances that traditionally triggered federal Schedule I enforcement of cannabis cultivation. This motivated prospective farmers to seek strains or cultivars that were suppressed or entirely absent for the genes expressing the psychoactive compounds. These were generally believed to be THC and CBN, and due to the ease of decarboxylation allowing ***in situ*** generation of these compounds, their corresponding acid precursors THCA and CBNA (where available, if at all). The target compounds, at the time, were CBD and its precursor CBDA. We have illustrated a cannabinoid schematic from 2014 in Imageδ to help give an approximate sense of the chemical perspective the industry was perceiving at that time.

Although Imageδ has many similarities to Imageα which was made in 2022, a noticeable difference is the absence of semi-synthetic cannabinoids and fully synthetic cannabinoids. While fully synthetic cannabinoids are not connected to the pathways of the natural cannabinoids; the semi-synthetics are. The biggest changes from the landscape presented in Imageα from those in Imageδ is the addition of two reactions: first, the CBD → Δ8THC reaction and, secondly, the HHC synthesis reactions. Both of the above reactions relate to the series of THC isomers known as the delta series (Δ).

The delta series was discovered when chemists observed that the double bond in THC can be re-arranged to several other positions. The natural THC isomer, the one produced by the plant, is Δ9-THC. As this double bond moves to other positions in its ring, it changes the delta number of the isomer. Originally it was believed that only Δ9-THC was psychoactive, but further investigation has shown that the other isomers in the delta series also show psycho-activity, although often with lower potency than Δ9-THC. As these THC isomers in the delta series are exposed to oxygen, the oxidation of each of them yields the same final



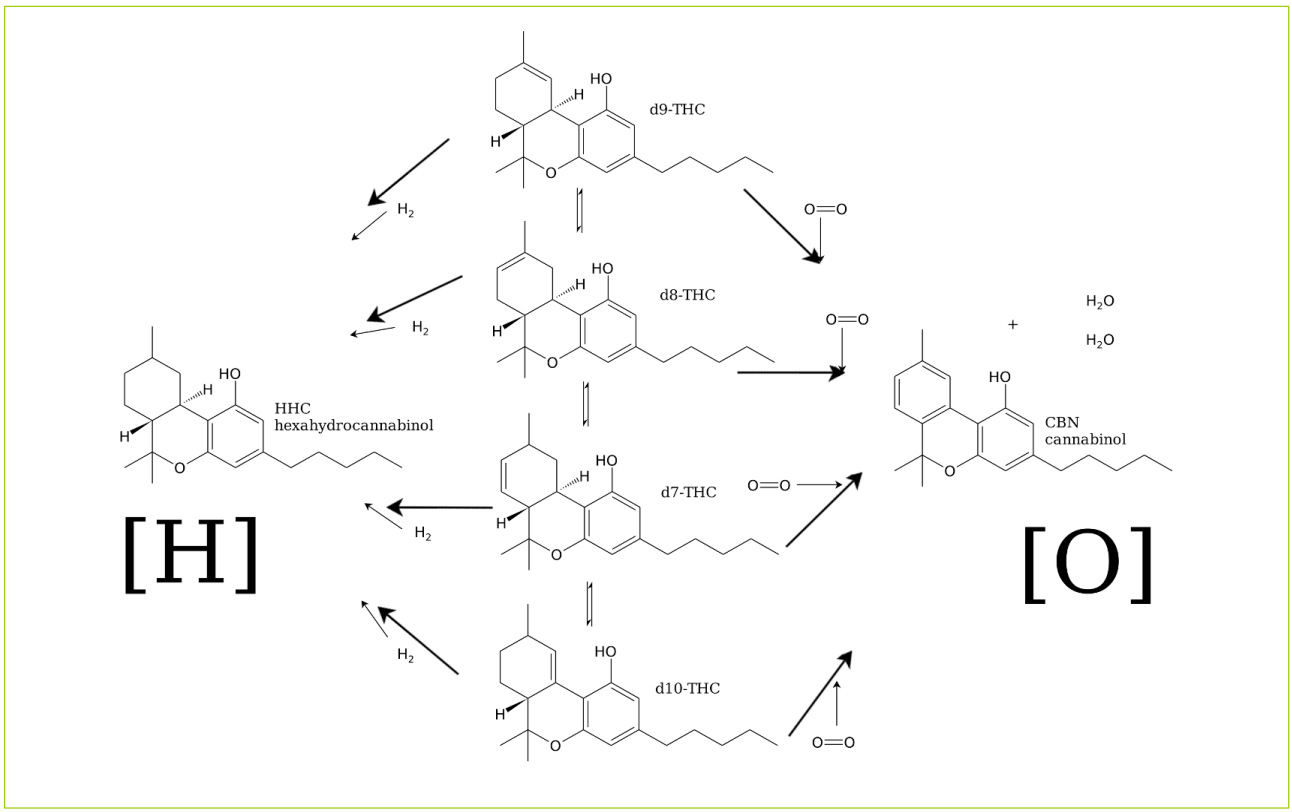
Imageδ – A skeletal diagram of the organic structures of the natural cannabinoids and their breakdown products from 2014, before California, Nevada, Maine, and Massachusetts recreational cannabis programs were passed by state legislators, and well before the U.S. federal government passed the 2018 Farm Bill. At that time, the CBD → Δ8THC reaction was not well known, and so the liability for psycho-activity for CBD producers was outlined as above, keeping THC-species separate from CBD or other non-psychoactive cannabinoid production. Note that chemical reactions, indicated by arrows, bear reaction names in this diagram. Image credit: Digamma.

product, CBN, regardless of which isomer from the delta series was the starting point. This is illustrated in Image**ε** for visual clarification with all reactants and products indicated, such as H_2, O_2, and H_2O.

What has changed significantly from 2014 to 2022 is the presence of a well-established class of reactions that can convert CBD to Δ8-THC. This is achieved through a variety of means but the most successful and popular reactions seem to use a Lewis acid as a catalyst. A Lewis acid is a type of acid that can temporarily store electrons, and this ability helps it to affect structural re-arrangements in a molecule. In particular, the Lewis acid helps to store electrons during the ring closing reaction that occurs between CBD and any THC isomer.

But this reaction rarely, if ever, produces Δ9-THC like the cannabis plant does naturally. This is because the Lewis acid's ability to affect structural rearrangement applies equally to both the ring closing reaction and the double bond rearrangement reaction. Due to this dual effect, the product of CBD ring closure is most commonly the Δ8-THC isomer. We have illustrated this reaction in Image**ζ** to help demonstrate the relevant components. What this reaction does in tandem is close the third ring on the THC isomer while also moving the double bond from the Δ9 to the Δ8 position. Why does the Δ8 position emerge as the exclusive (or most common) product of the reaction? The answer has to do with thermodynamic properties of molecules called conformation energies.

The reason that Δ8 is the major product of the CBD ring closing reaction has to do with the stability of the double bond in various positions. Each position that the double bond could potentially be in the ring has a different effect on the thermodynamic strain caused by the deformation of a geometrically idealized ring. The natural product, Δ9, causes a strain on the left side of the ring, and the corresponding double bond on the mirror image side, Δ7, shows a reflexive strain on the opposite side of the ring. This strain is often described by chemists as "puckering" to signify the deviation from the planar flat ring that would



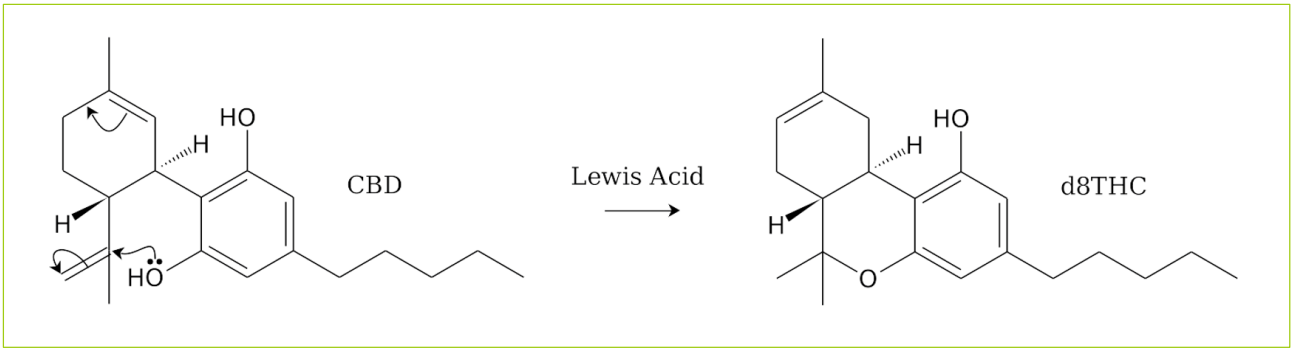
Imageε – A diagram illustrating the positions of the delta series of THC cannabinoid isomers in relation to two of their end-products: CBN, HHC. The first reaction shows the four isomers converting to CBN, the ***oxidation*** of 4H from each isomer in the delta series (right-facing). The second reaction shows the four isomers converting to HHC, the ***reduction*** of 2H into each isomer in the delta series (left-facing). Image credit: Digamma.

be the lowest energy state of the system. A chart showing the calculated thermodynamic energies of conformation for each THC isomer in the delta series combined with a three-dimensional illustration of the ring geometries with ring strain indicated is provided in Imageη.

Other than the conversion of CBD into THC delta series isomers, the other big innovation from the 2014 →2022 time period is the innovation of HHC, also known as **H**exa**H**ydro**C**annabinol.

The first reference to this compound was at the CannMed 2017 conference at Harvard Medical School Campus, where Mark Scialdone presented his creation of HHC, the process he used to make it from Δ9-THC, and how similar that process was to the process used by the food industry to convert plant oils into margarine. Scialdone confessed to smoking HHC experimentally to see what the subjective psychoactive effects where and to compare to Δ9-THC. When asked by one of the doctors in the audience what HHC felt like, he replied that it was similar to Δ9-THC but it made "his beard feel itchy" to a very distinctive cry of synchronized gasps from the largely clinically-trained audience in the lecture hall. Additionally, according to the discovering chemist, HHC was indeed a psychoactive substance.

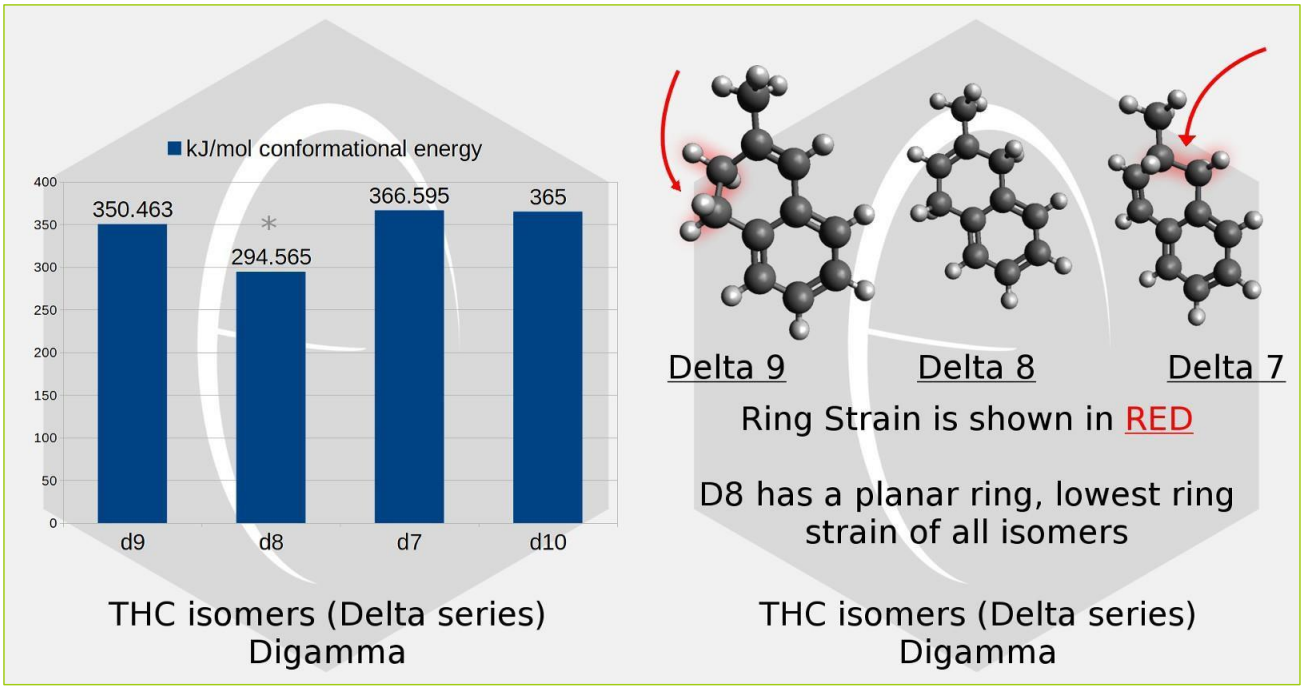
The chemistry of HHC is relatively simple to relate, especially when one has a good understanding of the relationship between CBN and THC, or **T**etra**H**ydro**C**annabinol. This name seems a bit odd, as the tetrahydro prefix makes it seem like a modification of an existing structure. The fact is that this is true because cannabinol (CBN) was discovered before THC, and so the root name of the structure goes to CBN as cannabinol. Because cannabinol has four hydrogens removed relative to THC, the proper name for THC was simply a cannabinol root with a tetrahydro- prefix attached. The fact that CBN is made through degradation of THC was not something initial



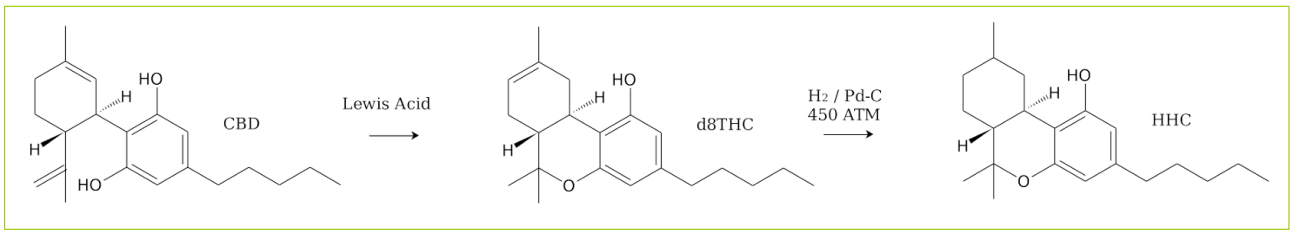
Imageζ – A diagram of the ring closing reaction that allows CBD to convert to Δ8-THC. This reaction is known to require a Lewis acid for effective yields. The Lewis acid, an electron acceptor, helps to close the ring in the reaction between CBD →THC, but also helps to cause the double bond re-arrangement into the Δ8 position. Image credit: Digamma.

scientists were aware of, as CBN is more stable than THC and early experiments most likely used old, processed (like hash), or cured cannabis products, which would have had a lot of THC that could have been oxidized to CBN. This is why the early experimenters identified CBN as the most abundant and stable compound and assumed it was the primary active ingredient in cannabis.

When Raphael Mecholaum published the first correct structures of THC and CBD in 1964 and 1965, respectively, both were shown to have a single double bond in the second ring in the Δ9 position. This explained why the natural cannabinoids have isomers in the delta series, which applies in parallel to both the THC and CBD isomer series. What this means is that all the delta isomers that



Imageη – Left: A diagram showing the calculated conformational energies of each THC isomer in the delta series. Right: A 3D illustration of the relevant geometries in each double bond position for each of the delta series, with ring strain indicated in red with a red arrow. Image credit: Digamma.



Imageι – A diagram of the ring closing reaction that allows CBD to convert to HHC through Δ8-THC. The second reaction requires gaseous hydrogen (H_2) with a platinum or palladium catalyst (platinum or palladium respectively). The first half of this reaction is shown in Imageζ. Image credit: Digamma.

exist for THC also exist for CBD and are known stable chemical structures, but CBG does not have delta isomers.

Adding two double bonds produces CBN, regardless of which isomer in the delta series was the starting point for the reaction. But what happens when the ring is stabilized not by completing the aromatic double bonds, but removing them altogether? This is the chemical structure of HHC, and like the production of CBN, it can use any THC isomer in the delta series as a starting point for its reaction. This concept was illustrated in Imageε previously for the reaction from THC delta series isomers to CBN and HHC. We have illustrated the reaction showing the anti-parallel reactions of oxidation (to CBN, right-facing) and reduction (to HHC, left-facing). Thermodynamically, CBN and HHC represent a downward and upward energetic step from the THC isomers in the delta series, both of which are stable endpoints for all the isomers in the delta series.

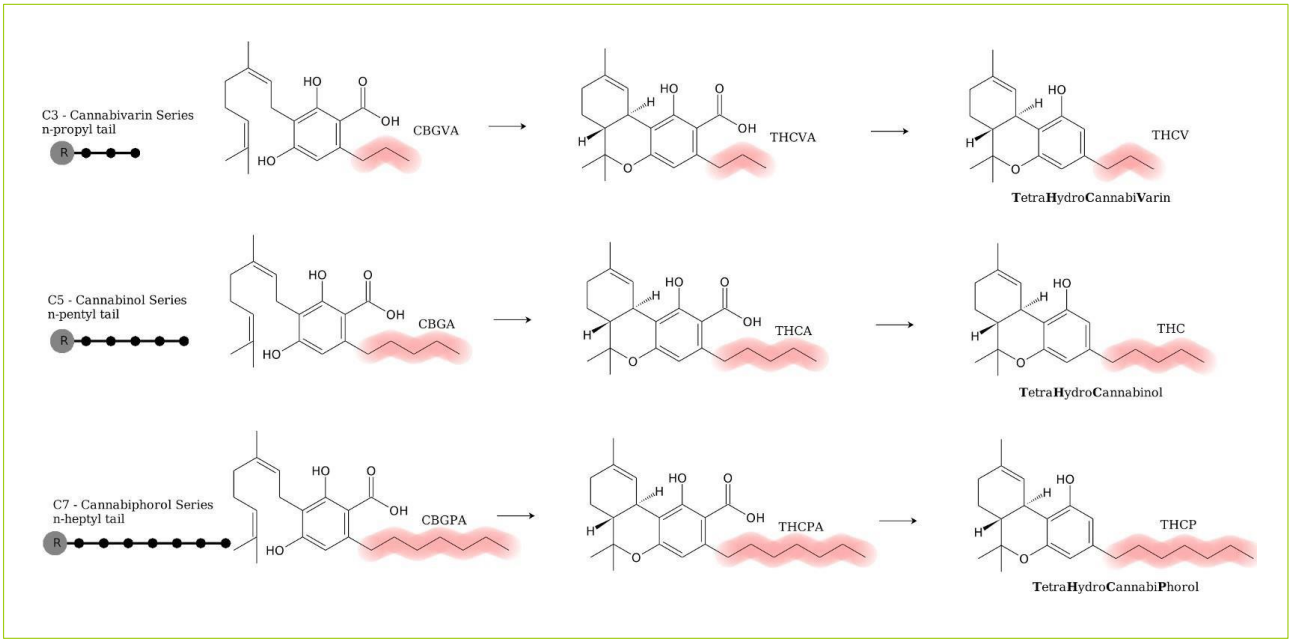
Returning our attention to the reaction outlined in Imageζ which shows how a Lewis acid can be used to catalyze a CBD ring closing reaction that produces Δ8-THC. When we combine the information in Imageζ with the information in Imageε, which showed how delta series can become HHC, we get a reaction starting with CBD and ending with HHC. We have reproduced this reaction mechanism in Imageι. The reaction, outlined in Imageι, uses the same technique used by the food industry to make non-spoiling margarine from plant oils. This conversion is done by catalytic hydrogenation with a platinum or palladium catalyst at several hundred atmospheres of pressure. This same process is used to convert a THC delta isomer to HHC.

What this reaction allows is for a producer with non-psychoactive compounds to convert to natural cannabinoids and semi-synthetic cannabinoids that are indeed psychoactive. The reactions outlined in Imageι allow a psychoactive cultivation system to exist that entirely bypasses Δ9-THC as a compound present on-site at a facility at any detectable concentration. The significance of the reactions from Imageι will be elaborated upon in the following section titled "Law" and more of the legal and business consequences of these implications will be discussed there. It is important to understand the chemical landscape from 2014, outlined in Imageδ, before studying the reaction mechanisms outlined in Imageι

What Imageδ does not have that Imageι introduces (and can be seen in Imageα) is a path from CBD to the THC delta series and therefore from non-psychoactive to psychoactive substances.

The final component of cannabinoid chemistry that must be covered is the pentyl tail analogue cannabinoids. Most traditional cannabinoids, such as THC, CBD, and CBG, have a five-carbon tail attached to them called a pentyl tail. When this tail is swapped out with a three-carbon tail, called a propyl tail, THC becomes THCV, CBD becomes CBDV, and CBG becomes CBGV. What THCV stands for is **T**etra**H**ydro**C**annabi**V**arin. The -varin ending indicates that the traditional pentyl tail has been replaced with a propyl tail.

When the pentyl tail is not replaced with the propyl tail but rather a seven-carbon tail called



Imageι – A diagram of the ring closing reaction that allows CBD to convert to HHC through Δ8-THC. The second reaction requires gaseous hydrogen (H_2) with a platinum or palladium catalyst (platinum or palladium respectively). The first half of this reaction is shown in Imageζ. Image credit: Digamma.

a heptyl tail, then the suffix switches from -varin to -phorol. THC becomes THCP, which stands for **T**etra**H**ydro**C**annabi**P**horol, with analogous names for CBDP and CBGP as well.

Although THCV is more well known in the cannabis community than THCP, which seems to be a more recent phenomenon, there are other pentyl tail analogues of cannabinoids that are known. THCO is the acronym given to the one-carbon tail analogue (this is called a methyl tail) and stands for **T**etra**H**ydro**C**annabi**O**rcol. Although many of these pentyl tail analogues are considered to be semi-synthetic, they have been known to occur naturally in cannabis plants for many years through THCV and the strain Doug's Varin. These isomers seem to be formed upstream from the formation of CBG and seem to be made upstream from the synthesis of olivetolic acid (OA) when the pentyl tail is added to the OA molecule. Although the genes that govern this are still not well understood, THCP, THCV, THCO and other pentyl-tail analogues that are reported to have various levels of psycho-activity are known to exist in the cannabinoid supply chain and do not formally meet the chemical definition of Δ9-THC. Evidence of THCV acting as an antagonist to Δ9-THC ability to stimulate appetite are known, making it an appetite suppressant. Data on THCP seems to indicate the elongation of the pentyl tail has the reverse effect as shortening, with a stronger cannabinoid binding strength of THCP to the CB_1 receptor relative to Δ9-THC.

We have illustrated the biosynthetic pathways for THCV, THC, and THCP respectively from top to bottom in Imageκ. The carbon tail is illustrated by diagram on the far right, and the CBG →THCA → THC pathway is illustrated for each.

Now that we have covered the relevant chemistry that governs these cannabinoids, we can progress to the legal implications of these compounds and how they are regulated and legally distributed at this time.

LAW

The laws surrounding cannabis are complex and spread over a rather long history, so the information has been organized chronologically to help create a linear narrative on the evolution of cannabis laws in the U.S. Both federal and state laws will be included with the most relevant state laws on the evolution of the cannabis legalization phenomenon being given an emphasis.

Marihuana Tax Act of 1937

The marihuana Tax Act was one of the first federal laws to regulate cannabis in the U.S. This act taxed cannabis and was drafted by Harry Anslinger, the commissioner of Federal Bureau of Narcotics. This act stayed in effect until it was repealed in 1969 and replaced by the Controlled Substances Act the following year. Although this act established the federal prohibition of cannabis with the main justification being the psycho-activity of the cannabinoids it produces.

Although this law can be seen as one of the foundational elements of the prohibitionist laws and enforcement throughout the second half of the 20th century often called "the war on drugs", it is believed that the motivation behind the bill was to stop the growth of the industrial hemp industry. William Randolph Hearst, a newspaper magnate who was riding the "yellow journalism" wave to great success, was heavily invested in timber to supply the pulp for his newspapers and feared that the growth of the hemp industry would threaten both his timber investments and his media empire. Andrew Mellon, then secretary of the Treasury, had invested heavily in Du Pont's newly patented chemistry process for making stronger, synthetic fibers from petrochemicals called "nylon". Both individuals had strong financial reasons for the hemp fiber industry to either fail or stagnate.

Regardless of the reason, the importance of the 1937 act is that it established for a generation that the federal government had the right to tax and prohibit certain substances. Young people growing up in the period between 1940-1970 were internalizing a system of drug prohibition. By the year 1970, a pattern of prohibition was accepted as established practice by late 20th century Americans.

Controlled Substance Act of 1970

The Controlled Substance Act (CSA) of 1970 is a foundational document in the establishment of widespread drug prohibition in the late 20th century American history. The bill itself was signed by President Richard Nixon and created several familiar elements of drug prohibition, including the drug category system known as "scheduling" of controlled substances, as well as a federal agency called the Drug Enforcement Agency (DEA).

Before 1970, federal drug issues were handled by two agencies, the Bureau of Narcotics and Dangerous Drugs (BNDD) and the Office of Drug Abuse Law Enforcement (ODALE). The FDA received recommendations from both agencies on May 1, 1970, for scheduling of controlled substances in the CSA Bill. Shortly after, on June 1, 1970, Nixon combined the two agencies to form the DEA.

Part of these joint recommendations from the DEA-FDA input was to assign schedule numbers to each controlled substance. There are three components considered when assigning a schedule for a drug, the first being its potential for abuse, the second is the presence of accepted medical uses, and the third consideration is the factors of safety and addiction. Depending on the risk factors in these three categories, the drugs are assigned a schedule number, starting with I as the most prohibitive with no accepted medical use, and schedule V as lowest potential for abuse.

Much like the marihuana Tax Act of 1937, the CSA was a federal strategy to bring national unity to a problem that had significant diversity in law and enforcement on the local level. While many states in the early 20th century passed laws regulating and taxing both the hemp and marihuana forms of cannabis, it was not until 1937 that a federal law unifying the national landscape came about. The CSA in 1970 functioned much in the same way, creating sweeping federal precedent for the patchwork of local drug enforcement laws at the state level. As the CSA was being passed

through Congress, the Justice Department under John Mitchell was authoring and sharing drafts with justice departments of state-level versions of the CSA with very similar language and legal structure as the federal bill. This not only established a unified federal code for prohibition and enforcement of drug laws, but also established agreement between federal and state policy surrounding controlled substances in the U.S. This intention, to have federal and state law in complete alignment, is the exact opposite of what has happened in the modern legal scenario with the Cole Memorandum of 2013, discussed below, where state and federal laws are in direct contradiction.

The important legal consequence to focus on is the schedule system that was created in 1970. Schedule I substances, such as heroin and LSD, have no accepted medical use and are known to have high potential for abuse and addiction. In the original text of the CSA, Schedule I substances are listed under section 202 sub-section (c) where hallucinogenic substances are covered, and "Marihuana" is listed as item 10. One method of relating the three terms for cannabis is that the first is the species genus name, and marihuana and hemp are terms used to describe that species cultivated for drug and fiber cultivation respectively.

The consequences for listing a plant species among a category designed and inhabited by molecular species are significant and not readily evident. Other residents of the Schedule I category are popularly known substances, mostly as illicit drugs, but are always listed as a chemical compound and not as a biological species. LSD was listed above and is a part of the tryptamine class of compounds. Tryptamines are compounds that mimic the serotonin structure and target its 2A receptor sub-type, among others, and typically induce a psychedelic experience in users. Other tryptamines on Schedule I include psilocybin and psilocin, the active ingredients in Psilocybe species and other closely related mushroom species, sometimes called magic mushrooms.

Psilocybe mushrooms are an excellent comparative example to cannabis in the legal language of the CSA. The other Schedule I substances listed in the above paragraph were each molecular species, a specific chemical compound. With Psilocybe mushrooms, we see the active ingredients listed as chemical compounds regardless of the biological source and the biological species associated with them. If Psilocybe mushrooms were listed in the same manner as cannabis, the text would read something like "magic mushrooms". A more scientific name would be "***Psilocybe cubensis***" or "***Psilocybe mexicana***". Instead, the CSA continues with a pattern of criminalizing chemical compounds and not biological organisms, except in the case of cannabis or "Marihuana".

If the CSA had consistent language for cannabis as it did for other Schedule I residents, then the compounds Δ9-THC, CBN, and any other cannabinoid that is considered an active ingredient to the recreational consumption of cannabis would be listed. Such legal language would have automatically excluded all non-psychoactive compounds discovered in that same organism, whether discovered before or after the bill's signing. In the example of cannabis, this would apply to CBD and the other non-psychoactive cannabinoids. But the inclusion of the term "Marihuana" makes this interpretation difficult.

Additionally, references to THC are made in the CSA on line 17 with "Tetrahydrocannabinols." The term tetrahydrocannabinols is somewhat ambiguous, as it seems to reference the THC delta series due to the use of plural. This language also seems to exclude psychoactive substances such as CBN and HHC, which are not "tetrahydrocannabinols", as well as the non-psychoactive substances such as CBD and CBG. The original language has been amended to "Tetrahydrocannabinols, except for tetrahydrocannabinols in hemp (as defined under section 1639o of title 7)". This change is a reference to the 2018 federal farm fill, which is covered later in this section.

Even infamous drugs that have caused social harm around the world, such as cocaine and methamphetamine are placed on the Schedule II category in the CSA. This is because there are medical uses that can establish the accepted medical component of the scheduling decision, even if the abuse and addiction elements are very

unmanageable. A medical application for eye surgery protects the Schedule II status of cocaine. When compared to other topical anesthetics in the same chemical class, such as lidocaine and Novocain, cocaine molecules have a better outcome with the nerves of the eye, and so an application is medically justifiable for ophthalmic surgery. Much like cocaine, methamphetamine is included in Schedule II rather than Schedule I because of its links to an FDA-approved drug called Desoxyn (generic is called methedrine), which is prescribed to children as young as six years old for symptoms relating to Attention-deficit/ hyperactivity disorder (ADHD). Juvenile pharmacology will make another appearance in the following two sections, covering California's first medical cannabis program in the U.S. and Colorado's first recreational cannabis bill, as the need to give juveniles with seizures caused by Dravet syndrome a safe and reliable source of CBD.

Proposition 215 (CA 1996)

Proposition 215 in California was the first medical cannabis initiative authored by a state government in contrast to federal prohibition. The bill had many authors, including Dennis Peron who was an activist advocating for the use of cannabis to treat the HIV/AIDS crisis that was impacting the San Francisco Bay Area. After passing with 55% of the popular vote in 1996, clarifications and administrative considerations were expanded in Senate Bill 420 in 2003.

The new Californian system was simple enough: if anyone had an "herbal recommendation" from a doctor, they were allowed entry into medical dispensaries to purchase cannabis. The doctor needed to be properly licensed and willing to give an "herbal recommendation" for cannabis for the patient's health, a document that was valid for one year and cost usually under $100. Finding doctors who were willing to formally recommend cannabis was difficult at first, but then a system emerged where doctors who advocated for cannabis would advertise herbal recommendations for practically anyone who made an appointment. Symptoms as general as anxiety and insomnia were acceptable, creating an accessible system.

The term "herbal recommendation" is a contrast to a prescription, which is connected to controlled substances and their classification under the federal system. Instead, the doctor is merely recommending a natural herbal remedy based on symptoms, and that document justifies entry, purchase, and possession of cannabis according to the laws of California, in a sort of federal by-pass. Other peculiarities of the California medical system included a cooperative system where cultivation facilities were actually collectives. Members' rights to grow plants were essentially transferred over to the collective who organized a large grow and distributed the harvest to the members. What this often became was a dispensary where first-time members would have to register as part of the collective before walking in and shopping, which followed the practical retail model but was legally still a collective of medical patients who simply did not have the time or resources to cultivate their own medical plants.

Apart from issues in the business structure of the growing medical cannabis industry in California, the legal aspects were being contested between federal and state authorities. This led to many state-legal cannabis operations being raided by federal DEA agents and the operators arrested under CSA violations. The case of Oakland Cannabis Buyer's Cooperative even made it before the Supreme Court in 2001, which ruled in favor of federal authority to schedule substances and enforce federal law.

With this precedent in place, an era of federal raids on California cannabis operations began. The federal prosecutor Melinda Hague was routinely pursuing the big-name Bay Area cannabis dispensaries, such as CBCB (Cannabis Buyers Club Berkeley) and Harborside in Oakland, to name a few. The Cole Memorandum of 2013, covered in a section below, brought an end to federal enforcement on state legal operators in practice for a time.

The success of cannabis in treating HIV/AIDS patients in San Francisco in the late '80s brought about a pharmaceutical product, Marinol, which is a synthetic Δ9-THC preparation in sesame oil, for treatment of HIV/AIDS wasting syndrome and a few closely related syndromes. In 1986, the DEA rescheduled Marinol from Schedule I to Schedule II. It was found that many of the other broader benefits of whole plant cannabis were not seen

in Marinol, which showed clinical effectiveness only with the wasting syndrome and stimulating the appetite. This evidence pointed to a possible entourage effect in whole plant cannabis that may not be transferable to the isolated components.

Amendment 64 (CO 2012)

With the advent of recreational cannabis bills passed in 2012 in Colorado and Washington, the cannabis industry changed again as the medical necessity of consumers was no longer necessary for purchase of cannabis. Dispensaries were now simply carding consumers at the door like bars to verify they were over 21, which opened the door to much wider markets for these dispensaries. Colorado being surrounded by states with more prohibitive laws, was seeing cannabis tourists boosting its industry revenue and state tax revenue was sharply rising. It is possibly at this time that the "green wave" concept of a rising and profitable industry started to become cemented in the public perception.

But as the industry expanded and cultivation and dispensaries became a common sight in Colorado, the proliferation of breeding stock and cultivation experiments led to many sought after CBD rich strains becoming known. This coincided with a growing recognition within the cannabis industry of a form of juvenile epilepsy called severe myoclonic epilepsy of infancy (SMEI) or Dravet syndrome. This disorder causes severe seizures starting in infancy which often progress and become worse, causing a large number of seizures often numbering in many per day. The seizures are so common and disruptive that normal growth and development of the child is impaired and often results in life-long severe disability.

What was discovered was that high doses of CBD stopped many Dravet-related seizures, in some cases with such effectiveness that seizures would almost cease and the child could resume normal development. But because isolated CBD was not widely available at that time outside of Colorado, many families with children with Dravet syndrome had to relocate to Colorado to treat their children. A famous example is Charlotte Figi, the patient who gave her name to the strain Charlotte's Web, which was a high CBD, low THC cultivar intended to treat children with Dravet syndrome.

Given the miraculous nature of CBD to reverse the course of a disastrous disorder, it seemed that the acceptance of CBD in mainstream medicine was the natural next step. And GW Pharmaceuticals received approval for Epidiolex, a CBD oral preparation for Dravet syndrome, and rescheduled Epidiolex (but not CBD) as a Schedule V substance. This allowed physicians to prescribe the product to patients within federal law but left the legal status of CBD even more nebulous at the federal level.

Additionally, studies have shown that CBD alone is not sufficient to stop all forms of seizures in Dravet syndrome patients. Some studies from Israel have shown some other rare cannabinoids that are co-present with the CBD extract that are necessary for the final effect, which are often absent from the pharmaceutical preparation of Epidiolex. The studies discovered these rare and trace level cannabinoids when following the outcomes of a juvenile patient who was receiving CBD extract from a local grower, whose crops had slight genetic drift from harvest to harvest. The scientists were able to identify that this drift lost these trace components and was correlated with the return of the seizures in the patient. This is similar to the lack of efficacy the pharmaceutical industry experienced when patenting THC as Marinol for HIV/AIDS wasting syndrome, and both examples indicate the entourage effect as the most likely explanation for the effects lost from whole-plant cannabis and its extracts.

Cole Memorandum of 2013

The Cole Memorandum effectively ended the federal enforcement of federal cannabis law against state legal programs. The new Justice Department policy stated that distribution of non-medical cannabis would be tolerated in states where it was legalized, except were firearms or interstate commerce were involved. This put an end to the raids and legal battles that state legal operators had to contend with and was a big step towards the legitimization of cannabis business.

The effect was reinforced through the Rorhabacher-Farr amendment the following year. The amendment prohibits the Justice Department from spending funds on the enforcement of federal cannabis law on state medical cannabis programs. The amendment expires annually and must be renewed every year, and last expired September 20, 2022.

Attorney General Jeff Sessions rescinded the Cole Memo in 2018 but few prosecutions have been seen from the DEA since. The Rohrabacher-Farr amendment, if it continues to be renewed, will prevent an Attorney General hostile to state legal cannabis from taking significant action, as it most likely had done in the case of Sessions' tenure and its lack of federal raids.

Recreational Bills of 2016 (CA, NV, MA, ME)

This section covers a tipping point in the political climate of the U.S. cannabis industry. In November 2016, four states, including the largest by population and GDP, legalized recreational cannabis at the state level in the footsteps of Colorado and Washington. Mainstream acceptance of recreational cannabis was at a tipping point, where a phenomenon seen while stopping over in Denver was now seen on both U.S. coastal population centers.

After this moment, a return to federal enforcement seen under the Bush administration during the early days of California's medical system was no longer politically tenable. Attorney General Jeff Sessions, incoming with the Trump administration after November 2016, was infamously hostile to cannabis and was quoted saying, "Good people don't smoke marihuana". In alignment with that philosophy, he promptly rescinded the Cole memo in 2018. But aside from the above-mentioned Rohrabacher-Farr amendment from Congress blocking Sessions from using a single dollar for a raid on a state legal cannabis operation, the political climate in the U.S. had shifted. Although finally in the political position to stop the legalization phenomenon, Sessions, as the Attorney General, no longer possessed the political capital to carry out such actions.

Farm Bill of 2018

Leading up to 2018, the legal situation for various cannabinoids was becoming both fluid and confusing. CBD had been rescheduled to Schedule V but only as the Epidiolex formulation, and yet CBD products were sold online and in smoke shops in all 50 states. The terms in the CSA, "Marihuana" and "Tetrahydrocannabinols" seemed to not cover CBD as a controlled substance, but the FDA had not approved it as an ingredient in food or supplements. A lot of the CBD seemed to be sourced from hemp farms that were allowed under clauses in 2014 Farm Bill, such as allowances for Indian Tribes and universities performing research. But as the amount of CBD being produced through hemp increased dramatically in the years since 2014 and 2018, a comprehensive solution was necessary.

This is where the 2018 Farm Bill changed things by defining hemp. The definition of hemp in the Farm Bill is included in the opening line of Title X Horticulture, Sub-section G Hemp: "The term 'hemp' means the plant *Cannabis sativa* L. and any part of that plant, including the seeds thereof and all derivatives, extracts, cannabinoids, isomers, acids, salts, and salts of isomers, whether growing or not, with a delta-9 tetrahydrocannabinol concentration of not more than 0.3 percent on a dry weight basis."

When compared to the more nebulous terms in the CSA, the Farm Bill seemed to be very clear-cut. It defined a specific molecule, Δ9-THC, as the active ingredient that would make a cannabis plant a controlled substance, the CSA's "Marihuana". The amended language in the CSA also notes that "Tetrahydrocannabinols except those derived from hemp" seems to exclude any cannabinoid that was sourced from hemp from the CSA.

"*Cannabis sativa* L." as it appears in the Farm Bill is categorized as a legitimate biological species. The language describes the Latin binomial name derived from Linnaeus' biological classification system from the 18th century. In fact, the capital

L. after many biological species names is a reference to Linnaeus' name and indicates that they are one of the species named in his 1735 publication of *Systema Naturae*, a scientific text that proposed a taxonomic system for classifying plants, one that is still used today. But unlike the CSA, the Farm Bill identifies biological species with a precision that the more cultural term "Marihuana" does not. Additionally, it defines hemp as a biological species with a condition of a certain chemical concentration, which is a much more precise legal and scientific definition. As covered in the section on the CSA above, the terms hemp and marihuana are used to express human intent when cultivating the same species of plant, *Cannabis sativa* L., making them imperfect definitions for legal status as they are tied to the cultivators' intent and, by implication, the breeding history of the cultivars, rather than a chemical concentration that can be measured and used as evidence in court.

Additional clauses in the Farm Bill shed light on some of the legal regulations that apply to hemp products that cannot apply to state licensed cannabis products. The authority to change other laws, such as the CSA, which has added a reference to the first section of the Hemp Sub-section G defining hemp, is included in 7 U.S. 1639r. The right of inter-state transportation for hemp products is defined in Section 10114, which explicitly states that nothing in the Farm Bill prohibits inter-state commerce of hemp or hemp-derived products [7 U.S. 1639t]. These changes are in direct contrast to the lack of progress many politicians and activists have had to implement for natural cannabinoids like Δ9-THC. These clauses support the direct contrast that is being seen in federal hemp versus state cannabis enforcement, with the right of inter-state commerce being a very significant advantage over state cannabis operators.

But with the laws being set up in this way, many producers could cultivate CBD producing plants and then convert them into psychoactive substances other than Δ9-THC, not triggering the enforcement of the CSA. A law that was passed for industrial hemp and non-psychoactive cannabinoids such as CBD was now giving semi-legal federal status to producers of psychoactive cannabinoids, such as Δ8-THC and HHC, as they were classified as hemp derived in the laws.

This created a wave of Δ8-THC gummie producers who sold their products in smoke shops and online across the 50 states. Many expected federal raids from the DEA or cease-and-desist letters from the Justice Department or the FDA. But instead a federal court ruled that Δ8-THC was legal if derived from hemp. In May 2022,making a ruling on *AK Futures LLC v. Boyd St. Distro, LLC*, the Ninth Circuit Court of Appeals decided that the Farm Bill defines hemp derived Δ8-THC as federally legal. This ruling took away the threat of federal enforcement against producers of hemp-derived psychoactive cannabinoids and allowed the growing federal recreational hemp market to keep expanding.

But the legal status of Δ8-THC with the FDA is still uncertain. It seems that like the FDA's perspective on CBD applied to Δ8-THC as well, that any marketing for medical conditions would be illegal until after GRAS applications and much evidence-based data. GRAS stands for **G**enerally **R**ecognized **A**s **S**afe, an important FDA status for a compound to be considered "safe". It seems that being defined as outside the CSA but not yet within the FDA GRAS list puts both CBD, Δ8-THC, and other cannabinoids in a gray zone between criminal enforcement and accepted medical use.

Where the FDA seems to feel very differently between Δ8-THC and CBD is in the psycho-activity. Whereas CBD's non-psychoactive properties make it less concerning when the market expands rapidly across the U.S. the proliferation of Δ8-THC has essentially brought recreational cannabis to all 50 states overnight. The FDA has reports of the dangers of Δ8-THC marketed as a "legal high" and is concerned about the harsh chemicals needed to transform CBD into Δ8-THC.

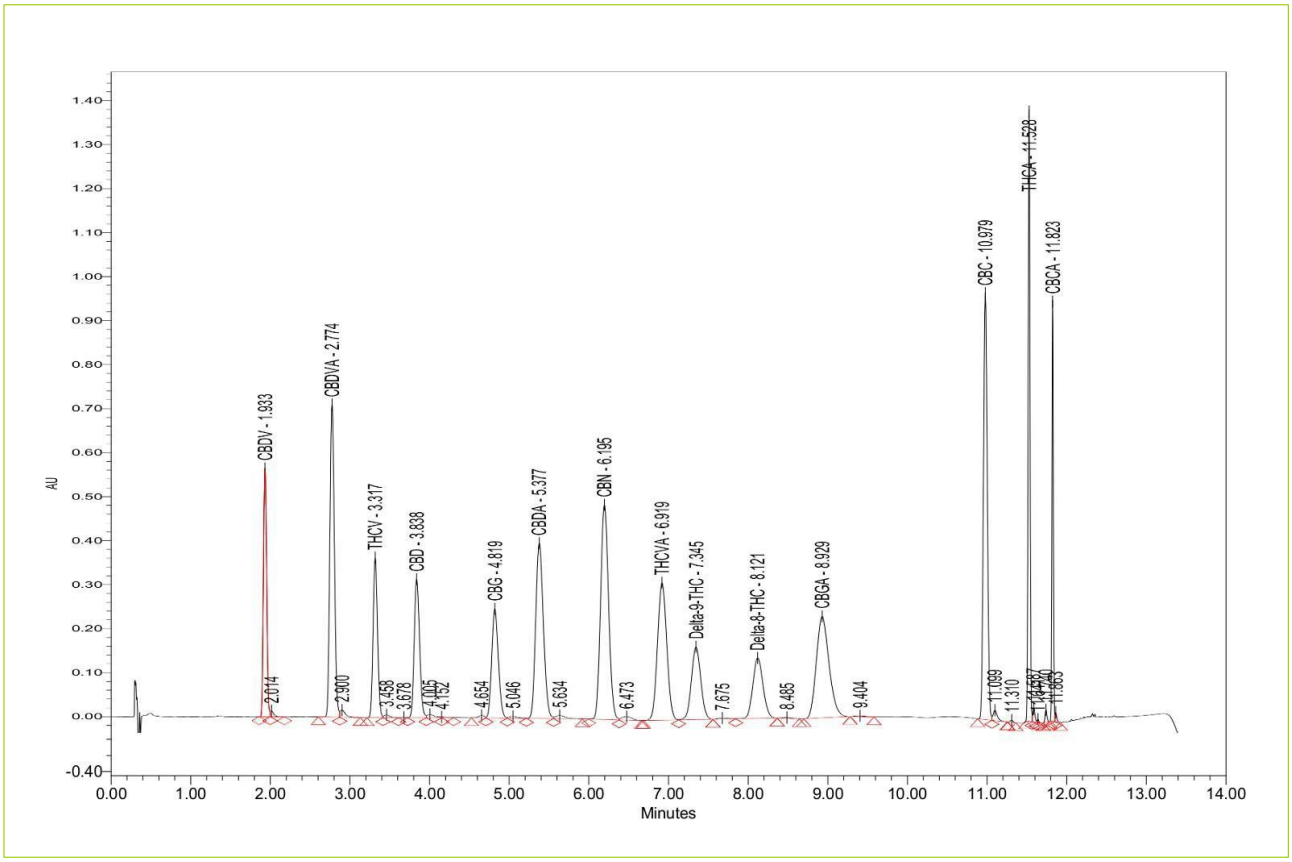
The FDA is correct about safety concerns, as the supply chain for recreational hemp Δ8-THC products looks very different from a state-licensed dispensary's process for making Δ9-THC products. In the following section, which focuses on chemical analysis for safety and labeling, these issues are covered. Labeling is a process with ramification for the legal status of products that must be defined as "hemp" or "marihuana" under federal law.

ANALYSIS

This section is about the analytical chemistry done on hemp and cannabis products. There are several elements that relate directly to business and law aspects of the cannabis industry that are covered in this section. We start with chromatography and how compounds are separated, with an emphasis on the distinction between Δ8- and Δ9-THC. The separations are followed by matrix interferences, which can interfere with accurate quantification of a compound, and the standard quality control used in the analytical chemistry industries to combat such sources of inaccuracy. The section closes on the testing requirements for state cannabis compared to federal hemp, with an emphasis on the differences in safety and contamination testing. A deep understanding of how analytical chemistry instrumentation works is not within the scope of this section but references to such works are included.

The best place to start is the chromatograph, the output of the analytical instruments that perform the analysis. Each separated compound is shown as a Gaussian peak separated along the horizontal x-axis. In Imageλ we have shown a 14-cannabinoid chromatograph showing the separation of pure calibration standards at the same concentration, with each peak labeled by individual compound.

Because the separation of compounds is critical to accurately measuring them, the separation of each peak from the next is an essential component of an accurate analysis. This is called baseline resolution, when peaks are completely



Imageλ – Above is a chromatogram of a 14-cannabinoid analytical assay performed on calibration standards of equal concentration for each cannabinoid. The chromatogram shows the instrument detector responding to each compound as it elutes from the separation column. The retention time of each compound, in minutes, is indicated on x-axis label. From a Waters Acquity with a TUV detector from a state cannabis lab in Missouri.
Image credit: Digamma.

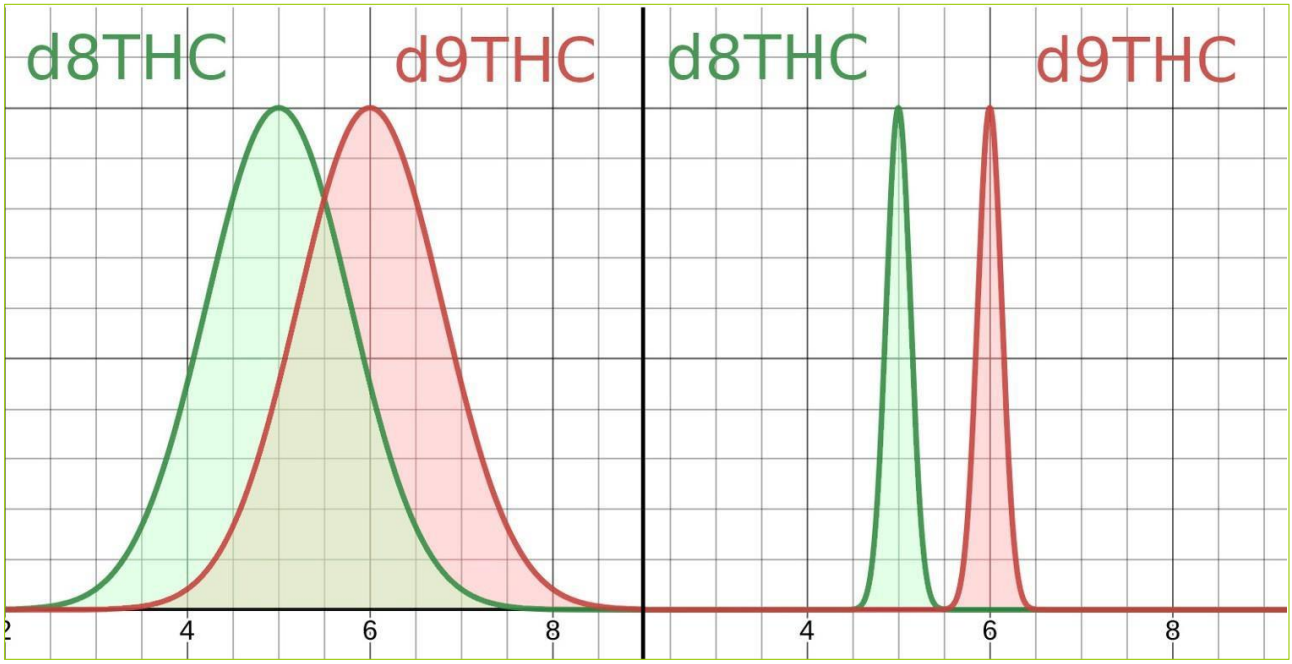


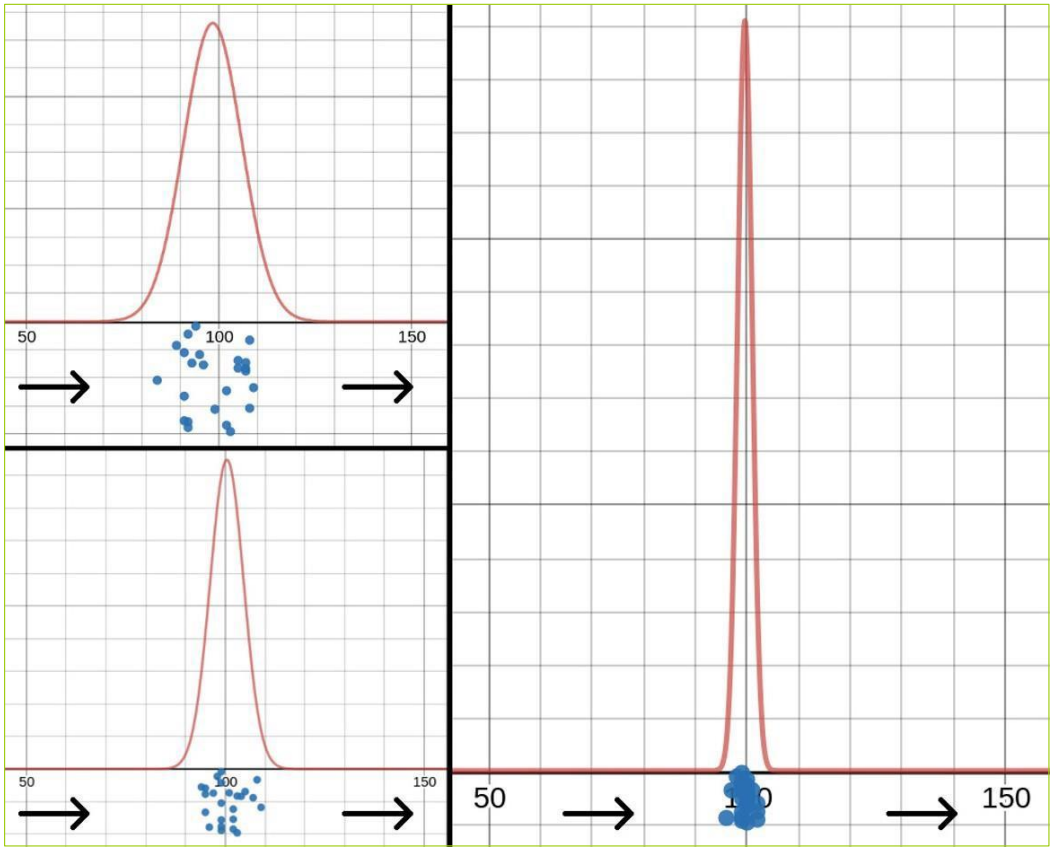
Image μ – An illustrative example of the effect of chromatographic resolution on separating structurally similar chemical isomers. The examples used here are the isomers of THC in the Δ8 and Δ9 form (labeled in **green** and **red** respectively). The image to the left shows a low-resolution separation where the two compounds co-elute (overlap) and cannot be independently measured with accuracy. The image to the right shows the same isomers with the same retention times, but with much higher chromatographic resolution, causing the peaks to elute separately (no overlap). Image credit: Digamma.

separated down to the chromatograph baseline. Achieving baseline resolution between very similar compounds, such as Δ8- and Δ9-THC, can be difficult and may require more advanced instrumentation. Chromatographic resolution is defined as the width of the Gaussian peak, and so an increase in resolution describes a decrease in peak width. In Imageλ the highest resolution is seen at the beginning and end of the chromatograph with a lower resolution peak in the middle of the graph around minutes 7-9.

Insufficient resolution can cause improper measurement of the target compound if they overlap with each other. The overlapping of chromatographic peaks is called co-elution and is a known issue in analytical chemistry. In Imageμ, an example of two co-eluting peaks, Δ8 and Δ9, are shown with low followed by high resolution. In the low-resolution image, the two compounds co-elute and the accurate measurement of either peak is no longer directly possible, as the overlap interferes with the total quantity. Additionally, teasing out two separate concentrations for two compounds is nearly impossible if the peaks are not fully separated. In the high-resolution rendition, the peaks are resolved to a much higher resolution and are much tighter, giving baseline resolution between them allowing for the accurate measurement of both compounds. To better understand how labs achieve high resolution and accurate measurement of cannabinoids, we look at the spatial distribution of target compounds in the instrument.

As the target compounds are separated from each other, they are distributed spatially in the chromatographic column in a diffuse cloud. When the cloud becomes more spread out, the peak becomes lower and wider, with lower resolution. As the cloud becomes densely compressed, the peak becomes taller and tighter, with higher resolution.

The tightness of the compound grouping can rely on many factors, as was illustrated in the

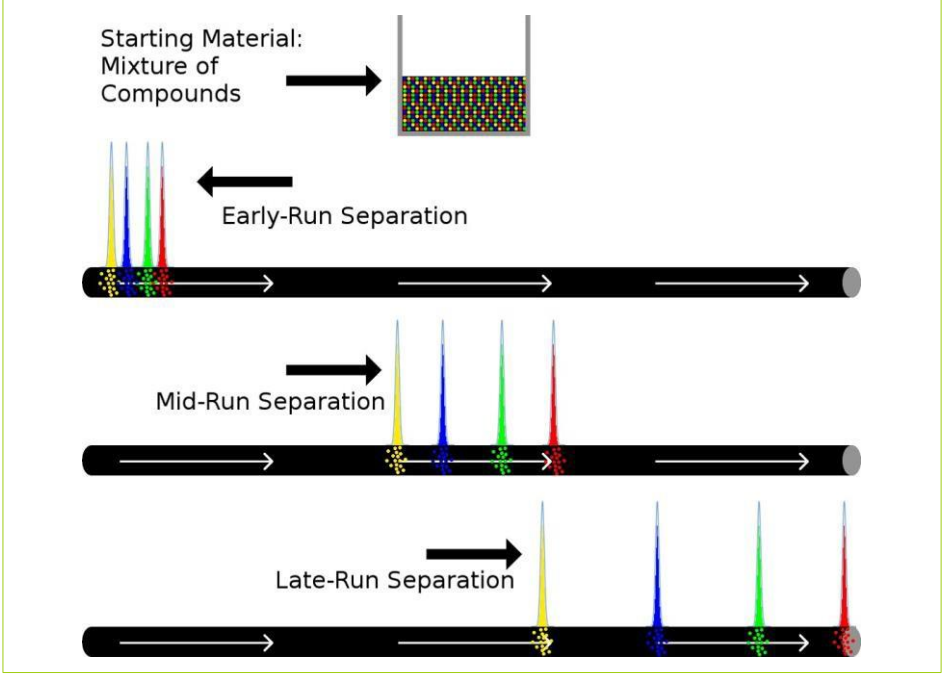


Imageν – An illustrative example of the relationship between chromatographic resolution and the compound distribution. The diagram relates a Gaussian function in **red**, showing the detector signal over time, and the distribution of compound particles in the column, shown in **blue**. The tighter the distribution of particles in the column, the higher the chromatographic resolution of the Gaussian curve read by the instrument's detector. Image credit: Digamma.

chromatograph in Imageλ to vary across the length of the chromatograph. This is because the rate of elution varies through the chromatographic run, changing the distribution of particles and thus the Gaussian peak shape. These subtle variations are dependent on the specific analytical method that a laboratory is running, but as long as all target compounds are baseline resolved the results are equivalent within an acceptable margin of error. To examine how we can increase chromatographic resolution across the entire chromatographic run, we will have to examine the chromatographic column and the variable of its length.

To understand the effect of column length on chromatographic resolution, it helps to start with this understanding: because the column separates compounds, the longer the column, the better the separation of compounds and therefore resolution. To help illustrate this effect, we have shown the separation of model compounds in a mixture in Imageξ. What this image helps to illustrate is that longer columns may be necessary to separate very close compounds, like the delta series of THC isomers.

Aside from co-elution of target compounds, another major interference on the accuracy of a reported lab result can be matrix interference. Matrix interference is a Gaussian chromatographic compound just like the target but is defined as a non-target compound present in the sample matrix (or substance or material). When these compounds co-elute with target compounds, the measured peak may be under-reported or missed altogether (false negative). The matrix interference can often be under much lower resolution with

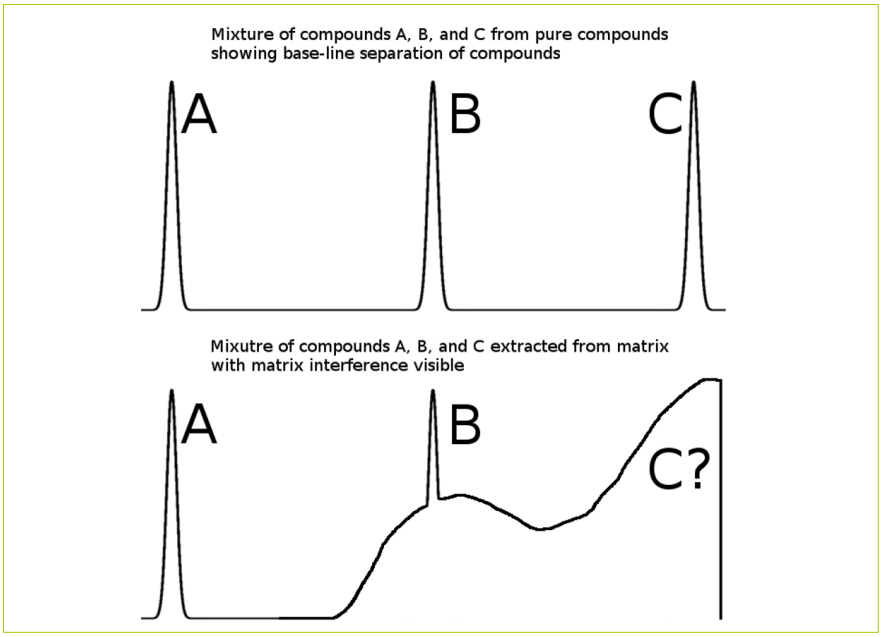


Imageξ – An illustrative diagram showing how chromatographic separation works in theory, as applicable to both gas (GC) and liquid (LC) chromatography. The mobile phase is contained within the column and shown in as black tubes, with the mobile phase passing through it as while arrows. The diagram shows how the column separates four compounds, **yellow**, **blue**, **green**, and **red**. The compounds travel through the column with variable resistance and become organized from an even mixture (pictured on top) to perfectly separated compounds eluting from the column (pictured on bottom). The diagram also illustrates how the chromatographic resolution increases with column length. Individual particles with an approximate spatial distribution are shown within the column with Gaussian peaks simulating the detector signal resting on the top of the column. Image credit: Digamma.

broad, sometimes meandering, curves. This widening of matrix effects is often because the analytical method was optimized for target compounds, which come out in high resolution, but other substances may not be under optimal conditions and may form these broad shapes.

The way analytical labs combat these effects on the accuracy of the data is by having quality control that shows a lack of interferences and that all target compounds are being detected with accuracy. There are many complex terms in the quality control world of analytical chemistry labs, such as quality management system (QMS), laboratory information software (LIMS), as well as validation and method development. The process certifying the accuracy of an analytical lab is quite a rigorous process, made more challenging by cannabis specific legal restrictions. State labs must seek a license from the state department regulating the cannabis program, and often seek an ISO 17025 accreditation as well. Cannabis labs have two choices in ISO 17025, Perry Johnson Laboratory Association (PJLA) and American Association for Laboratory accreditation (A2LA). Federal hemp labs are also required to have a DEA anti-diversion license after January 1, 2023, which mostly focuses on the ability to safely receive and store-controlled substances with a minimization of risk of diversion to the community.

What we have reproduced below with Image[1] is a sample of a certificate of analysis from a cannabis lab reporting on 11 cannabinoids. The rows colored in green are quality control (QC) samples that are run as part of the QMS. These include blanks to rule out false positives (PB and MB), positives or spikes to rule out false negatives and under reporting, and some calibration verification before and after the client samples to prove accuracy throughout the run (ICV and CCV) with a final blank at the end to rule out



Imageo – An illustrative example of how interferences can affect the quantitation of certain compounds in chromatography. In the top, compounds A, B, and C are shown eluting with more than baseline resolution. In the bottom we see the presence of an interfering signal from non-target compounds cover up part, as in compound B, or all, as in compound C, of a detected peak. Image credit: Digamma.

cross contamination. Many regulated analytical chemistry industries require a calibration check after every 10 client samples to re-verify calibration and demonstrate accuracy of all samples in the batch without exception. The FDA and EPA have similar requirements in place, as well as specific version of the matrix QC samples run at the beginning of the batch.

Now, many state cannabis programs have requirements modeled after the EPA and FDA guidelines. But, ultimately, federal chemistry guidelines cannot apply to an industry that is illegal under federal law. So, what has happened instead is that each state government has put its local staff on the task of researching chemistry regulations and drafting a series of requirements that is modeled on federal standards but is authored by the state legislature and enforced with state authority exclusively. This scenario creates a regulatory patchwork where each state has slightly different versions of similar requirements and enforces them differently.

One such state is Nevada. Back in 2015, the state's Department of Public and Behavioral Health used the code of federal regulations to find action levels for pesticides in cannabis. Because the Nevada departments did not feel they had sufficient medical authority to actually make that determination, even in the form of citing the most appropriate example in a comparable industry, they went with a policy of using the lowest stated limit for any food item in the CFR as the level for cannabis, guaranteeing they were not setting a higher limit than would be warranted. Although many changes have happened to Nevada regulations since then, this was the process of authoring analytical chemistry regulations for the state licensed cannabis program.

The state of California, which began the same process two years later in 2017, had significantly more resources at the state and community level. Meetings were called for public input on proposed regulations and committees were formed with scientists and doctors who were familiar with analytical chemistry regulation. The levels and tests being set seemed more reasonable and to be authored by a more informed community of professionals and volunteers, and so a big improvement over the counter example of

	LOD (% w/w)	0.0055	0.0050	0.0093	0.0075	0.0073	0.0077	0.0075	0.0088	0.0080	0.0071	0.0076
	LOQ (% w/w)	0.0504	0.0460	0.0851	0.0688	0.0674	0.0704	0.0692	0.0812	0.0734	0.0649	0.0695
Sample Name		**CBDV %**	**CBDA %**	**CBGA %**	**CBG %**	**CBD %**	**THCV %**	**CBN %**	**d9-THC %**	**d8-THC %**	**CBC %**	**THCA %**
PB - Prep blank		<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ
MB - Matrix blank		<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ
LCS - Lab Control Standard		<LOQ	<LOQ	<LOQ	<LOQ	98.84%	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ
LRS - Lab Replicate Sample		<LOQ	<LOQ	<LOQ	<LOQ	4.49%	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ
ICV - Indepdent Cal Verification		91.78%	101.73%	100.00%	101.07%	100.04%	105.27%	99.65%	97.11%	98.31%	103.74%	101.70%
Sample 01 10X		ND	<LOQ	12.59	<LOQ	ND	ND	ND	ND	ND	<LOQ	0.13
Sample 02 10X		ND	<LOQ	12.39	<LOQ	ND	ND	ND	ND	ND	<LOQ	0.11
Sample 03 10X		ND	<LOQ	11.37	<LOQ	ND	ND	ND	ND	ND	<LOQ	0.13
Sample 04 10X		ND	0.17	8.84	0.07	<LOQ	ND	ND	ND	ND	<LOQ	0.13
Sample 05 10X		<LOQ	9.13	0.42	0.11	2.17	<LOQ	ND	0.18	ND	0.27	0.21
Sample 01 200X		ND	ND	13.17	ND	ND	ND	ND	ND	ND	<LOQ	ND
Sample 02 200X		ND	ND	13.04	ND	ND	ND	ND	ND	ND	ND	ND
Sample 03 200X		ND	ND	12.28	ND	ND	ND	ND	ND	ND	ND	ND
Sample 04 200X		ND	ND	9.30	ND	ND	ND	ND	ND	ND	ND	ND
Sample 05 200X		ND	9.75	ND	ND	2.17	ND	ND	ND	ND	ND	<LOQ
CCV 50ppm		100.20%	100.34%	100.25%	99.68%	100.48%	100.62%	100.84%	100.87%	102.33%	101.07%	101.02%
CCB		<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ

Imageπ – A reproduction of a certificate of analysis (CoA) reporting on 11 cannabinoids, with quality control (QC) samples indicated in **green**. The green rows are known QC checks that help rule out the possibility of reporting errors by the lab. Image credit: Digamma.

Nevada was forecast. Many issues came out with enforcement and administration, the role of the then Bureau of Cannabis Control and now the Department of Cannabis Control (DCC) of California. The department had a high turnover of employees and turnaround of applications, and many of the staff were young and inexperienced and the office seemed understaffed to serve the size of the industry in California. Additionally, although conversations were well informed and fluid with the PhDs and MDs in the 2017 committees, by 2019 the enforcement of written codes and regulations were enforced according to department (or bureau) policy.

As different states issue their own testing regulations for state-licensed cannabis labs, different jurisdictions may have very different testing requirements. Although all states have amended their regulations over time to converge on an approximation of federal standards, some states skipped pesticide testing, some skipped microbiological testing, some had no heavy metal requirements, and other saw residual solvents as a test conditional on the solvents disclosed by the operator. But as the states begin to converge on standard cannabis testing regulations, a model that incorporates all solvents, pesticides, metals, and micro-contaminant assays is slowly emerging. The list of analytes, sometimes called the monitoring list, varies significantly between states but has been converging with amendments over time, much like the tests required in each state are converging. A summary of state and federal testing requirements has been shown in Imageρ.

Notice that in the federal requirements right now, only cannabinoid analysis is a requirement, along with moisture because of the fact that the Farm Bill stated the 0.3% Δ9-THC limit on a dry weight basis, so moisture will need to be known in hemp samples to give final results on a dry weight basis. Other than this, all the other requirements that apply to state-licensed cannabis labs do not apply to federal hemp labs, and so the consumers of federal hemp products are without the safety screening that is standard in state programs.

	Potency			Contaminants			
	Cannabinoids	Terpenes	Moisture	Solvents	Pesticides	Metals	Micro
State Labs	TRUE	TRUE	TRUE	TRUE	TRUE	TRUE	TRUE
Federal Labs	TRUE		TRUE				

Imageρ – A chart showing the analyses performed by cannabis analysis labs across states. Notice that federal labs are only required to test cannabinoids and moisture, making them a significantly less resource-intensive operation to establish than state-licensed cannabis labs. Image credit: Digamma.

		State Labs	Federal Labs
Potency	Cannabinoids	$20,000.00	$20,000.00
	Terpenes	$30,000.00	
	Moisture	$1,000.00	$1,000.00
Contaminants	Solvents	$50,000.00	
	Pesticides	$200,000.00	
	Metals	$65,000.00	
	Micro	$12,000.00	
	Total	**$378,000.00**	**$21,000.00**

Imageσ – A chart showing the relative costs of the median cost of used equipment as a comparison between the requirements on capital investment. Notice that the retail prices of new equipment would be between three to five times higher. Image credit: Digamma.

This puts consumers of federal hemp products at risk of contamination in their supply chain that is not possible from state-run dispensaries. This is a major safety concern for the public which the public may not be aware of.

There are additional factors that affect patient or consumer safety which are not applicable to medical and recreational cannabis at the state level. We covered these chemical reactions in the chemistry section; they were called Lewis acids. The catalysts that help turn the delta series into HHC were platinum or palladium metal catalyst fused with activated carbon. Both of these reagents are toxic to human health and are traditionally used by large pharmaceutical or other chemical process plants, which have strict protocols for removal and residual monitoring. At the moment, the recreational hemp market has no checks in place other than those voluntarily paid for at operator expense. These products that are being smoked and ingested by consumers may have small or even large amounts of residual toxic catalysts in them that reach the consumer and have negative consequences on their health. Federal safety tests could include many common catalytic reagents that may be present at residual levels in the final product.

In addition to the concerns for public health, there are also concerns about free market and fair play principles. When we look at the median cost of used equipment and compare the approximate cost of starting a state cannabis lab and a federal hemp lab, the cost is over 10 times higher for a state lab. With 10 times higher costs, these labs are caught in a small state market due to the ban on inter-state commerce. Federal hemp products, however, are legal in all 50 states, allowing distribution on a much wider market. When these factors are combined with the higher tax penalties the state cannabis operators have to contend with, the gap in fair play between state cannabis and federal hemp operators is pretty wide at the moment.

CONCLUSION

As the FDA policy and commentary has made clear, it is taking a position of advising extreme caution among the public in using recreational hemp products like the delta series and HHC. Unlike the legal gray zone with CBD years earlier, these compounds are clearly psychoactive and their unregulated widespread distribution would be a broad public health crisis. The FDA has a more long-term nebulous stance on CBD, with bizarre exceptions like rescheduling the Epidiolex oral spray formulation as a Schedule V substance while keeping CBD itself in a nebulous state between being a Schedule I component of marijuana and being unscheduled through the Farm Bill. The FDA is likely to take more rapid action to regulate the recreational hemp cannabinoids than it has taken on CBD.

But FDA involvement may not be negative for the fate of these cannabinoids, even if it may remove them from the recreational hemp phenomenon. If any of these structures or their derivatives show improved efficacy in treating conditions over traditional medicines, they could be scheduled in the FDA system and be made available through prescriptions. Conversely, the opposite of this effect could happen and follow the "spice" products that use fully synthetic cannabinoids, many of which have toxic properties not present in the natural cannabinoids. These products caused a lot of overdoses and emergency room visits about ten years ago, before many of the more dangerous compounds being used in them were banned by federal authorities, as well as a series of bans from state governments such as Kentucky, Texas, and Florida. So, the fate of FDA involvement with this current phenomenon is still very uncertain.

The implementation of contaminant tests, which would most likely need to be at the federal level, would most likely not come out of FDA scheduling as the process for studying and evaluating a potential drug is well defined and would not follow the organic growth of testing regulations as was seen in the state medical and recreational cannabis programs. It is possible that the USDA or another agency that has more lax supply chain policies may implement some sort of standards of both potency and contaminants, including contaminants specific to the semi-synthetic cannabinoids and their catalysts.

Nearly everyone watching the recreational hemp phenomenon is predicting that the current status quo cannot last long. But as a large industry is growing around these compounds and is in direct competition with the state licensed cannabis operators, federal lawmakers may find themselves between two difficult choices. One is to continue to allow the state cannabis industries to be undercut, and the other is to allow federal progress and doom the new industries that have grown nationally to vanish overnight. Regardless of the outcome, a change is almost certainly coming soon.

September 12th, 2024
Cannabis Advisory Committee (CAC)
California Department of Cannabis Control (DCC)
2920 Kilgore Road
Rancho Cordova, CA 95670

Dear CAC,

We are writing this letter today to propose a solution to a growing issue in the cannabis industry: cannabinoid fraud through adulteration of natural cannabis with synthetic cannabinoids derived from hemp. This issue has been known to occur in California, but press shows this phenomenon is occurring in Colorado and Michigan as well, with many more suspected cases in other jurisdictions.

What this document outlines is a proposal to implement the ability to test for synthetic compounds derived from hemp by the state government, either through their cannabis reference lab or other analytical laboratories at the state's disposal.

Sincerely,

Marco Troiani
CEO
Digamma Consulting

Marc Whitlow
CFO
Digamma Consulting

PROPOSAL: SYNTHETIC THC DETECTION

SCOPE AND BACKGROUND

As the 2018 Farm Bill defined hemp in the federal jurisdiction, many cannabis plant cultivators have moved into federal jurisdiction by growing hemp instead of drug-type cannabis (popularly called marijuana). This has created a boom of less regulated and cheaper hemp products, such as CBD. As CBD prices drop, some manufacturers have found processes for converting CBD into psychoactive cannabinoids, most prominently delta-8-THC and HHC.

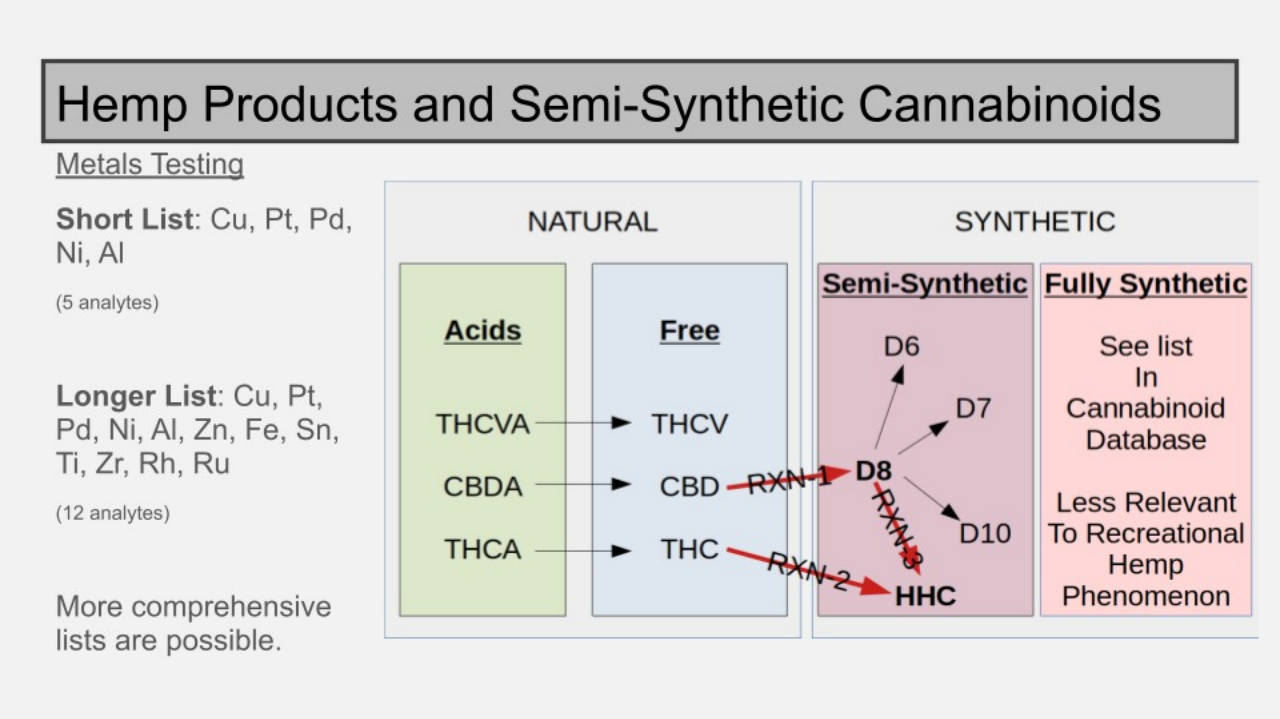


IMAGE01

As state governments have begun banning these products, the supply chain of CBD precursors have begun to pivot to synthetic d9-THC which is then smuggled into the state regulated medical and recreational natural cannabinoid market. This can be stopped by a very low cost test that can be run on the state's reference lab for virtually no additional cost. This proposal outlines these testing methodologies and explores some of those details.

ANALYTICAL METHOD PROPOSAL

Overview and Methodology of Chemical Testing

Products will be collected together for analysis and samples will be submitted to a qualified laboratory for analysis of cannabinoid content. The standard analytes that cannabis testing labs report may be insufficient for this study, which is interested in chemical markers of synthetic hemp products. Please see the sections below for an explicit outline of the experimental data needed to draw the conclusions put forth by this study.

Hemp Products and Semi-Synthetic Cannabinoids

Organics Testing

Organic testing on final products can confirm hemp conversions were used.

Chiral verification of **(-)-trans-Δ^9-THC** is best scientific option, but hi-cost (**$$$**).

Compounds listed here can be analyzed with existing instrumentation to indicate hemp source.

	COMPOUND	NATURAL LEVELS	IS IT HEMP?
1.	Δ^8-THC	Trace amounts	Conditional
2.	THC-O-Acetate	Trace amounts	Conditional
3.	iso-THC	None detected	Yes
4.	HHC	None detected	Yes
5.	Δ^6-THC	None detected	Yes
6.	Δ^7-THC	None detected	Yes
7.	Δ^{10}-THC	None detected	Yes
8.	THCP	None detected	Yes
9.	Δ^9-THC	Significant amounts	No
10.	CBD	Significant amounts	Not Necessarily
11.	THCV	Significant amounts	Not Necessarily
12.	CBG	Significant amounts	Not Necessarily
13.	CBN	Significant amounts	Not Necessarily

IMAGE02

Chemical Analysis

Chemical Analytes of a concentration will be required from the candidate analysis laboratory. For each analyte listed, a stated LOD and LOQ value complete with original concentrations must be stated. For further considerations regarding the quality of chemical analysis, see the “Laboratory Qualifications” section below.

Laboratory Qualifications

For a laboratory to be a suitable candidate to perform this analysis they must meet the following criteria. For the criteria of analytes available please see “Chemical Analysis” section above.

1. The laboratory must have current ISO 17025:2017 accreditation for the cannabinoid analysis being utilized in this experiment.
2. The laboratory must have a validation that demonstrates the following:

    1. Derivation of and declares the value of Limit of Detection (LOD) and Limit of Quantitation (LOQ) for each analyte being analyzed.
    2. Matrix-matched blank and spike recovery data to show a lack of interference with data accuracy based on the sample matrix. Each matrix submitted to the lab for the purposes of this experiment should have this data from a method validation.
3. Current Quality Control (QC) logs that can show analyte accuracy over time (typically done on a quarterly basis), including the QC data that will be run in the analysis batch(es) that were used to analyze the samples submitted for this experiment. This data will be critical for defending the accuracy of the data once published.
4. (*optional)* A license to test cannabis from the state of Colorado Marijuana Enforcement Division (CO MED)
5. (*optional)* A license to test hemp from the Drug Enforcement Administration (DEA) under the 2018 Farm Bill

Data Interpretation

The interpretation of the data will be the most important part of this process and should be separated with a clear boundary from the chemical concentration analysis itself. The laboratory should report concentrations in physical SI units to the CO NERDS group, and then the chemical analysis experts should analyze the raw data and present it to the group:

1. Whether the sample is presumed to be adulterated with synthetic cannabinoids from hemp.
    1. This question hinges on the first data set with the standard column but the extended analyte list
    2. Lack of CBGA ratio within the standard range (10-90X)
    3. Lack of CBG ratio within the standard range (1-10X)
    4. Lack of d8THC ratio within the standard range (2-40X)
2. Whether the sample is confirmed to be adulterated with synthetic cannabinoids from hemp.
    1. A = (-)-trans, B = (+)-trans, C = (-)-cis, D = (+)-cis
    2. Raio of A:B:C:D of 4:0:0:0 is a fully natural confirmed
    3. Raio of A:B:C:D of 1:1:1:1 is a fully synthetic confirmed
    4. Ratios between items b and c above can be deduced into ratios of the natural and synthetic extract by subtracting the 1:1:1:1 ratio from the data (the synthetic component) and analyzing the remainder (4:0:0:0) as the natural component
3. Which reaction pathway is most likely for the presence of synthetic d9-THC.
    1. This topic is highly complicated and requires the input from both data from sections 1 and 2 of this list. A chart of synthetic cannabinoid conversions should be consulted to best help inform the synthetic pathway. As this is beyond the scope of this document it will not be inserted her, but is available upon request.

All values cited here are derived from the lab data from 937 sample set cannabinoid analyses on all-natural cannabis from 2015 and 2016 before the 2018 farm bill began to incentivize these synthetic cannabinoids. Additional data to inform these interpretation decisions would be welcome and strengthen the experiment's conclusions.

	THCA/CBGA	THC/CBG	THC/d8THC
Averages	49.01	4.13	19.51
Deviation	39.10	4.20	16.93
n=	836	77	3
Range-Lo	9.91	-0.06	2.58
Range-Hi	88.11	8.33	36.45

IMAGE03

On Chirality

The chiral test that distinguishes the natural optical isomer (enantiomers and diastereomers) from the other 3 forms is the best scientific test to verify that synthetic cannabinoids are present in the sample. This would only catch synthetically made d9-THC but it would show all 4 isomers at some concentration, whereas natural cannabis extract would only have 1 isomer. We have illustrated the stereochemistry below for clarification purposes:

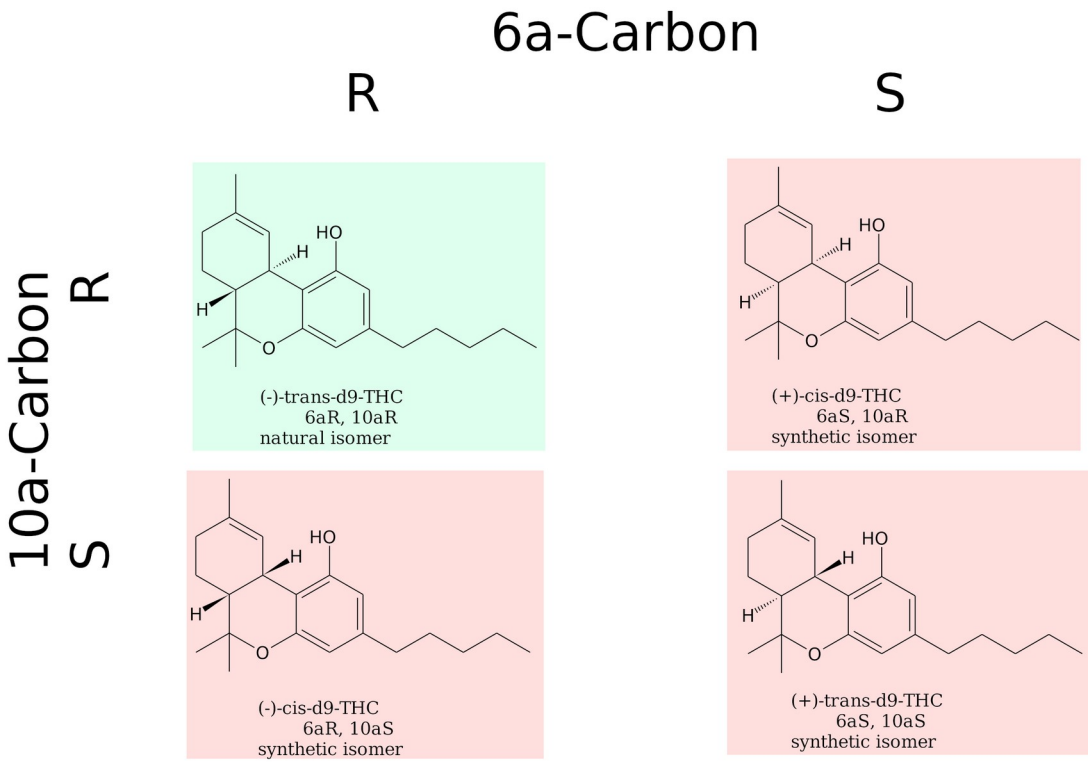


IMAGE04

The issue is that this test requires a more expensive column that is separate from the standard column used by most cannabinoid testing laboratories. The standard column cannot distinguish between optical isomers and will show a single peak for d9-THC which will be a combination of all isomers. It is therefore not capable of doing the optical isomer distinction that is needed for the scope of this study. If a laboratory is available to do this testing at a reasonable cost the study should utilize it. However, the experiment is designed to function in the absence of this chemical analysis which can distinguish optical isomers. See the “Data Interpretation” section above for more details.

Discussion and Enforcement

Once the state internally agrees about which samples contain adulterated active ingredients, the MED can make a consensus decision about how to best take enforcement action. This can be separated from the interpretation, which in turn should be separated from the chemical analysis. Although this process seems to weaken the conclusions, it actually strengthens it but giving a public and auditable review of the process used to derive these conclusions. This is analogous to legally defensible chemical analysis data produced in the laboratory, where a demonstration of standard practices and logical conclusions can strengthen the public acceptance of data or conclusions dependent thereupon.